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PUBLISHERS' ANNOUNCEMENT

THIS 1959 Progress Volume is the ninth of an annual series of supplements to *British Surgical Practice*. By this means the eight volumes of the main work are kept up to date in the ever increasing field of surgical knowledge, by original articles, critical surveys and abstracts

The Noter-up section will guide the reader from the main work to the supplementary material which appears in this or previous Progress Volumes. The purpose of the Noter-up remains the same as in previous years. The reader should first of all refer to the material in the main volumes of *British Surgical Practice*. Then, in order to ascertain the advances and changes which have been discussed in this or previous Progress Volumes, he should refer, under the same heading or key number as that consulted in the main work, to the Noter-up in the latest Progress Volume. There he will find details of the articles, surveys and abstracts relating to the subject which have appeared in the Progress Volumes. Regional or system surveys naturally cover a wider field than in previous volumes and individually apply to more than one chapter in *British Surgical Practice*. Because of this, the main subject headings within the surveys have been linked in the Noter-up to the appropriate chapter titles of the main work Thus by reference to the Noter-up, the reader of the main volumes is easily able to locate any new material on a particular subject even though it may be contained within a survey. The nature of surgical advance has necessitated the inclusion of new titles in the Noter-up, and for convenience and ease of reference, these are as follow: Abdomen; Anal Diseases; Antibiotics; Brain—Vascular Anomalies; Brain—Psychiatric Disorders; Carpal Tunnel Syndrome; Collagen Diseases; Electronics; Fluid and Electrolyte Balance; Gynaecology; Kidney and Ureter—Nephrectomy; Kidney and Ureter—Surgical Aspects; Liver—

Surgery; Lung—Surgery; Obstetrics; Organ Transplantation; Pelvic Organs—Viscerectomy; Pituitary Gland; Plastic Surgery —Correction of Facial Deformity; Thorax—Congenital Deformities; Ureter—Replacement of.

Non-subscribers will find the Noter-up section of value in that it is alphabetically arranged and gives at a glance information as to the presence or absence of recent material on any particular subject. Consequently, the book can be used independently.

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INTRODUCTION

THE APPEARANCE of this volume has been delayed by many misadventures including the printers' strike, but the most critical reader must admit that its twenty articles have been well worth waiting for. A few of them may seem to be rather highly specialized—for example, Halnan's on radioactive isotopes, Rycroft's on corneal grafting, and that by Ormerod and McLay on the plastic surgery of the sound conducting mechanism—yet many general surgeons must wish for information on all these subjects.

Now that hospital infection is such a generalized problem, and when autoclaves are under suspicion, Garrod's expert opinion and advice are particularly timely, and another of the special trends in modern surgery, the prominence of endocrinology, is shown in the articles by Selwyn Taylor, Carey, Welbourn, and John and Geoffrey Hadfield The natural tendency to regard endocrine disorders and endocrine therapy as somewhat obscure and therefore somebody else's business is counteracted by the clarity of exposition and the practical advice which characterize these articles. Furthermore, the account of the natural history of breast cancer covers the whole field and therefore embraces much more than the problem of hormone dependence.

Orthopaedics is well represented in the contributions of Pulvertaft, Matthews, Duthie and Sissons, and Gillis and Langdale Kelham, and here again there is a balanced mixture of theory (even medicine), pathology, and sound practical advice based upon experience. Somewhat akin to these articles is an excellent chapter on the Casualty Department by Ellis in which he shows the value of breaking with established practice and thus saving a great deal of time and disability in the management of abscesses and burns.

We are much indebted to Bruce and Card for a comprehensive critical review of peptic ulceration, and to Goligher for a masterly assessment of minor and major rectal surgery with most helpful technical detail. Lloyd-Davies and Hobsley give a first class account of the operation of partial hepatectomy largely based on the latter's own anatomical research. The review of pancreatitis by Birnstingl indicates the importance of obstruction of the pancreatic ducts in the evolution of pancreatitis and the frequency of carcinoma as a cause of this obstruction. Finally we welcome the chapter by Patey and Thackray on tumours of the parotid gland, which shows once again what good use they have made of their extensive experience of this disease, and the neurosurgical articles by Whalley and by Knight, the latter being a striking account of the operation of orbital cortex undercutting as an improvement on the standard leucotomy

There is wide variety and excellent quality in these articles for which we wish to express to the authors our sincere gratitude. The arrangement of the articles may appear haphazard and their titles a little odd, but this is the result of trying to make them fit into the headings of the subsections of the admirable work by Charles Rob and Rodney Smith on *Operative Surgery*. It has proved to be difficult to do this satisfactorily and the attempt is unlikely to be repeated

E. ROCK CARLING
J PATERSON ROSS

STERILIZATION BY HEAT

By L. P GARROD, M.D., F.R.C P.

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Heat is the most certain and the most exactly controllable means of destroying bacteria, and should be used for the sterilization of all surgical equipment which is not itself destroyed or damaged thereby. It has been too lightly assumed for many years that materials which have been exposed to heat in various ways, and particularly in an autoclave, are sterile, whereas for a great variety of reasons they may not be, and frequently are not. Inefficient steam sterilization may continue for years in a hospital without being detected. In order to comprehend this it must be remembered that two very different classes of bacteria are involved All those responsible for ordinary forms of sepsis are vegetative cells, and destroyed by moist heat at quite low temperatures, only the grossest defects in autoclave construction or operation can permit them to escape Fully efficient operation is necessary only for the destruction of spores, which have a far higher heat resistance. The only pathogenic spores likely to be present are those of clostridia, and since these are incapable of germination in healthy tissue, contamination of an operation wound by them usually has no effect. Were it not for this, so ubiquitous an organism as *Clostridium welchii* would present an appalling hazard; even *Clostridium tetani* was recoverable from 33 out of 50 large samples of operating theatre air (Lowbury and Lilly, 1958).

The fact that the risk of infection by heat-resistant bacteria is remote is no reason for condoning their possible presence in materials supposed to be sterile. The conscience of the profession has been thoroughly awakened by the results of studies made during the past 5 years which have shown that sterilization as carried out in many hospitals is inefficient At the same time increasing concern has been caused by the frequency of hospital infection, particularly by staphylococci, and in the effort to control this an overhaul of sterilization methods seems an elementary necessity

STERILIZATION BY STEAM UNDER PRESSURE

The principle of this process, admirably defined by Bowie (1955) and Perkins (1956), is that when dry saturated steam comes in contact with an object at a lower temperature it condenses, at the same time giving up its latent heat. The amount of this

is considerable; 180 British thermal units of heat are required to raise the temperature of 1 pound of water from freezing to boiling point, but a further 971 units are required to convert this amount of water into steam. Only a few more units of heat are added as the steam pressure rises (13·5 for the rise to 15 pounds per square inch), but the total is large, and it is the action of this heat, combined with the moisture produced by condensation, that sterilizes so efficiently. The speed of sterilization naturally depends on temperature; the necessary times at different temperatures (with their equivalent pressure of pure steam) as defined by Perkins (1956) are stated in Table I. It must be clearly understood that these data apply

TABLE I

TIMES REQUIRED FOR ABSOLUTE STERILIZATION BY PURE STEAM AT DIFFERENT PRESSURES

Pressure (pounds per square inch)	*Temperature* °F.	°C.	*Time (minutes)*
10	240	116	30
12	245	118	18
15	250	121	12
19	257	125	8
27	270	132	2

only to an atmosphere of pure steam, unmixed with air, and that for practical purposes the times apply from the moment when the load has attained the necessary temperature, the time taken to reach this may be 10–15 minutes or more for a bundle or drum of fabrics and still longer for large volumes of fluid, such as bottles of solutions for parenteral use With the exception of the last-mentioned, an adequate margin of safety for sterilizing any properly packed materials is provided by exposure to a temperature of 121°C. for 30 minutes.

Air discharge

Emphasis has been laid on the fact that the foregoing statements apply only to an atmosphere of pure steam. The presence of admixed air reduces the temperature attained at any given pressure (Table II) and is one of the commonest causes of inefficient working.

TABLE II

TEMPERATURES (C.) ATTAINED WITH DIFFERENT DEGREES OF AIR DISCHARGE*

Pressure (pounds per square inch)	*Degree of vacuum* *Complete*	*20 inch*	*15 inch*	*10 inch*	*None*
5	109	100	94	90	72
10	115	109	105	100	90
15	121	115	112	109	100
20	126	121	118	115	109

* As stated by Perkins (1956).

Air can be either pumped out or displaced. The principle of downward displacement is that air is heavier than steam (their respective weights at the same temperature and pressure being 0·12 and 0·07 pound per cubic foot); hence steam admitted at or near the top of the sterilizing chamber will expel air through a discharge pipe in its base. It is essential that the steam inlet should be at the top or side and the outlet at the lowest point, or an autoclave cannot function properly [illegible] charge pipe [illegible]. The most [illegible] ince of old autoclaves is to fit an automatic thermostatic valve in place of the manually operated valve This type of valve, referred to sometimes as a "balanced pressure steam trap" and representing perhaps the most important technical advance since pressure sterilizers were introduced, is illustrated in Fig. 1. Its moving part is a short concertina-shaped flexible metallic capsule containing a volatile liquid, the expansion of which by heat lengthens the cylinder and blocks the outlet to the discharge pipe Thus if what is escaping from the chamber is pure steam at the working pressure, this outlet will remain closed, if it includes air or condensate its

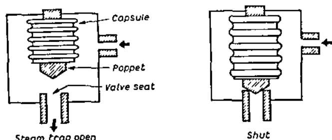


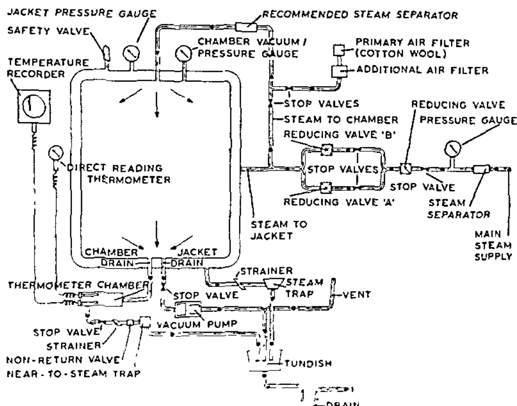
FIG 1 —Diagram of balanced pressure steam trap
(By courtesy of Dr J. H Bowie and the Editor of the *Pharmaceutical Journal*)

temperature will be lower and the valve will open Not all such valves are sufficiently sensitive, they should open if the temperature in the discharge pipe falls 2–3°F. below the working temperature of the autoclave. It may be added here that a most important item of equipment is a thermometer in the discharge pipe between the chamber and this valve. The temperature recorded by the thermometer should easily be read and preferably it should be continuously recorded graphically, as was pressure in the older type of record of a run A correctly designed autoclave fitted with these and other necessary attachments is illustrated in Fig 2

Preliminary evacuation of air

The preliminary evacuation of air may either be partial, as in most old autoclaves, or nearly complete, as in a few of the latest types A "partial vacuum" of anything from 5 to 20 inches, usually about 15 inches, can be "drawn" in most autoclaves In the operation of some a "double vacuum" is used, that is, some air is evacuated, steam is admitted and evacuation is repeated before the final admission of steam. These operations are not a substitute for the displacement of air by steam

by way of a thermostatic valve, they are only additional preliminaries. Such a partial vacuum has some advantage in aiding the displacement of air from the interior of drums and other large items in a load. Alder and Gillespie (1957) made some ingenious experiments in which the atmosphere within such items was



... downward displacement after ...
taining a thermometer, which may actuate both a dial and a recorder ... through the chamber ... emain open when ... liner is fitted on the ... ents of fabric. The ... e end of the period ... nd air is admitted ... nished by Mr. H.

sampled during a run, and found that these could be as much as 685 millilitres of residual air within a drum They compared the effect of simple downward displacement with that of a double 20 inch vacuum, and showed that the amount of residual air was much less with the latter system of operation, particularly when the packing or positioning of the load was unsatisfactory.

High-vacuum, high-pressure autoclave

A different proposition altogether is the new type of high-vacuum, high-pressure autoclave recently introduced on the Continent and now being manufactured in Great Britain (Bowie, 1958a, b). These machines have a relatively small chamber (the speed of operation being such that large loads need never accumulate) and a pump which will rapidly produce a vacuum of about 29½ inches. Steam is admitted at a pressure of 30 pounds per square inch (temperature = 134°C or 274°F.) and immediately penetrates the entire load, however it is packed or positioned: only a short holding period at this temperature is necessary. A further high vacuum is obtained, and air, so filtered as to ensure sterility, is admitted The whole operation occupies only 20 minutes, and is completely automatic; the nurse has only to load and close the chamber and press a button. For obvious reasons, this process is inapplicable to fluids, but is suitable for anything else, including gloves. This fact should finally explode the myth, perpetuated within the past 5 years in an official publication by the Ministry of Health (Report, 1954) that rubber gloves can only be autoclaved at pressures of the order of 5 pounds per square inch if undue damage is to be avoided. What damages rubber is not steam or heat *per se* within any reasonable range of temperature, but exposure to hot air, which presumably causes rapid oxidation. If air is eliminated, the highest temperatures used for other kinds of load will cause no undue deterioration.

This type of autoclave appears to be ideal, although perhaps more prolonged experience with it may be advisable before deciding how far it should ultimately displace other types. Wholesale replacement of existing machines would of course involve an immense outlay, and is quite impracticable. Autoclaves are not only very expensive, but very durable it is not uncommon to find them still in use after 50 years It is therefore our duty to inquire into the shortcomings of older machines, and into the possibilities of improving their performance

Causes of failure in steam sterilization

It has to be admitted regretfully that the general standard attained in Great Britain has hitherto been far behind that in the United States, Switzerland, Germany and some other Continental countries In the past this has been due to conservatism and ignorance on the part of manufacturers and users, economic difficulties have also played some part and must continue to do so.

The now classical *exposé* of defects in steam sterilization was that of Bowie (1955), who examined 64 dressing sterilizers in 45 institutions, and found only 5 of them to be fully satisfactory It is this paper that was responsible for the often quoted statement that 90 per cent of autoclaves in Great Britain are inefficient. This was followed by a similar survey conducted by Howie and Timbury (1956) with very similar results More recently a Report (1958) from the Nuffield Provincial Hospitals Trust has added to this evidence, but in a somewhat different sense: the major faults found were not so [illegible]
ignorant attendants. The [illegible]
be classified in three categ[illegible]

loss of efficiency, because superheated steam has the bactericidal properties of hot air and very poor penetrating power. If the materials were initially unduly dry (fabrics which have been in an atmosphere of average humidity contain about 13 per cent of water) or if they have been dried by the unduly long application of a vacuum before the admission of steam, superheated steam will cause them serious damage, a very high temperature being attained from the latent heat liberated by condensation on the dry fibres. In extreme instances of mal-operation, it is possible for a fabric load not merely to be charred, but to burst into flames when removed from the chamber, a paradoxical effect of exposure to water in its gaseous form which vividly illustrates the alteration in its properties produced by superheating. The effect of degrees of superheat commonly encountered, apart from the impairment of sterilizing efficiency, is usually no more than the fairly rapid deterioration of fabrics repeatedly sterilized.

Although according to the earlier work of Savage (1937) some degree of superheating does not prevent the destruction of spores by steam, it is probably unwise to allow the jacket pressure to exceed that in the chamber by more than 5 pounds per square inch, particularly in a small autoclave Undue drying of a load by a prolonged vacuum (usually the result of forgetfulness in manual operation) must obviously be avoided When the atmospheric humidity is very low, a condition uncommon in Great Britain but found, for instance, in the United States in winter when the indoor temperature may be 75°F. and the outdoor zero, fabrics may become unduly dry and need "hydrating" by spraying with water before being sterilized; under such conditions this is particularly necessary for gloves.

Operation includes maintenance—It is important to ensure by frequent inspection that the discharge pipe and the thermostatic valve in it are not clogged by fragments of fabric. Unfortunately some common faults are more elementary than this and due to the fact that autoclave attendants often have no understanding of the process for which they are responsible. Of 25 autoclaves inspected by the Research Team of the Nuffield Trust (Report, 1958) 9 were classed as inefficient, and the failure of 6 was "wholly or partly due to bad operation", consisting in 3 cases of keeping the chamber drain closed so that air and condensate could not escape, although the autoclave could have functioned satisfactorily from this point of view had it been operated properly. These revelations seem to demand that the status of autoclave attendants be reconsidered At present they are classed with porters, although paid a small extra sum for this duty They should perhaps be trained to carry it out more intelligently and be paid as skilled workers. The Report laid great emphasis on the necessity for supervision, an autoclave attendant should be responsible to some other official whose duty it is to see that his work is properly carried out These arguments may lose their force if and when all surgical steam sterilization is carried out in high-speed automatic autoclaves operated by nurses who need merely press a button.

The packing of loads

Nothing has been said hitherto about the packing of materials for steam sterilization, but this is a very vital factor in determining (1) whether the process is successful and (2) whether the load remains sterile after removal from the chamber.

Assuming that the load is permeable (clearly anything hermetically sealed cannot be penetrated by steam) the importance of the system of packing depends on the respective parts played by gravity displacement and vacuum in eliminating air. If an almost complete vacuum is attained, penetration must follow regardless of the system of packing and positioning, but in so far as downward displacement is the mechanism of air elimination, the importance of providing channels for the free flow of steam increases, and these should be aligned with the direction of its flow. Thus if drums are used, they should be placed on their sides to permit the passage of steam through their vents from above downwards, and materials within them should be layered so that steam can pass between the layers and has not to penetrat each of them to escape. Similarly if packs of fabrics are made up as bundles an not placed in drums, they should be so packed and positioned that the line of steam flow passes between layers and not through them; these packs should not be piled one above the other, but in such a way as to leave spaces between them. Any bowls, jars or cans should be placed on their sides so that steam can pass into and out of them; if the position is vertical air must pocket within them. Good and bad methods of packing loads are described and profusely illustrated in the works of Walter (1948) and Perkins (1956). The unduly tight packing of drums is a common cause of failure in sterilization. Alder and Gillespie (1957), who studied the effect of different systems of packing on both air elimination and sterilizing efficiency, mention a lightly packed drum the contents of which would fall out if it were inverted, and this might well serve as a criterion of how packing should be done.

Drums are seldom used in the United States, where sterilizing practice has fo some time admittedly been far ahead of that in Great Britain. They are roundly condemned in the Report (1958) of the Nuffield Trust, whose investigators found many examples battered, actually perforated, or with bent lids so ill-fitting that the contents were exposed. The fact that old and unserviceable drums are still in use is not a condemnation of drums as such; on the other hand, sterilizing efficiency is undoubtedly improved if a load is enclosed in porous material instead of metal. This Report suggested the substitution of disposable cardboard boxes, which have been shown to be well penetrated by steam, but nevertheless to protect their contents against subsequent contamination. The fact that cardboard is manufactured from dirty material and loaded with spores of clostridia (Editorial, 1958) is an aesthetic if not a practical objection to this proposal. Bags or wraps made of special forms of paper, nylon film or other materials have been used or suggested. This is a problem which might well repay further study, but there is much to be said for the widely employed American practice of wrapping in a double layer of suitable fabric, so folded as to exclude subsequent contamination from without.

Supervision and control of steam sterilization

An autoclave is a piece of machinery, and unless it is operated by someone of most exceptional intelligence, needs periodical attention from an engineer. There is much to be said for Howie and Timbury's (1956) dictum that before a bacteriologist tests the performance of an autoclave, an engineer should be called upon to verify that its design and installation are satisfactory and that it is in good working

order A suitably qualified engineer should be on the staff of any large institution, but this requirement may present some difficulty in a cottage hospital or nursing home.

Periodic tests of efficiency should certainly be made, although how searching and how frequent these should be is a matter of opinion, and may also depend on the basic efficiency of the autoclave itself, an old one operating near its margin of safety may need more attention than a modern one of first-class design. A test should not only determine whether sterilization is complete: it should verify that recontamination is not occurring at the drying stage by the admission of imper-
[illegible] ded which should
[illegible] al test of sterilizа-
[illegible] been placed in a
package in the centre of a drum or other least accessible point in the load. These spores may either be derived from a pure culture and dried on paper strips, or be those in crude material such as dust or dried soil If a culture is used it should be of a species and strain of adequate heat resistance and of sufficient age in a suitable medium to contain fully mature spores. Undoubtedly organisms of quite inadequate heat resistance have been widely used in the past Kelsey (1958) examined dried preparations of 25 mesophilic organisms (such as *Bacillus subtilis*) in use by other workers and found them all to be too easily killed On the other hand, he considered a test with *Bacillus stearothermophilus*, a thermophilic organism, or with soil, which may contain such organisms, to be too severe. For routine use he recommended Browne's tube No. 2, which he found to change colour only when exposed to an adequate temperature for an adequate time, whether a high temperature for a short time or a somewhat lower one for longer Howie and Timbury (1956) also recommended these tubes, but warned users that they should be stored at a temperature of less than 70°F or they may change colour too readily. They have the advantage of providing an immediate answer which can be read by anyone. They are naturally unaffected by atmosphere and therefore give results which are only significant if air discharge is satisfactory

Others dislike abandoning the use of cultures altogether, and while granting the remarkable reliability of the Browne tube, some authorities, for example, Report, 1958, prescribe additional tests with a standardized preparation of dried spores of *B. stearothermophilus* These are admittedly somewhat more resistant than those of the most resistant pathogen, *Cl tetani*, but this difference provides a suitable margin of safety

Finally, as so emphatically enjoined in the Report (1958) from the Nuffield Trust, an autoclave operator should be made responsible by a definite hospital rule to some other person whose duty it is to supervise this work. Whether this should be the bacteriologist, a surgical officer or the Sister in charge of Theatres might depend on local circumstances, but at least these men should not be left to continue what may be inefficient operation with no inquiry into what they are doing.

Instrument autoclaves

It has been standard American practice for some years to sterilize instruments in a special type of autoclave, and recently these have also been manufactured in

Great Britain. Since a high pressure is used and the load is fully exposed to steam, very rapid operation is possible, and a "run" need occupy no more than 6 minutes. The instruments are autoclaved in a perforated metal tray which can if necessary be immediately conveyed to the operating surgeon. American practice also includes the use of "washer-sterilizers" in which used and soiled instruments are cleaned with a hot detergent and subsequently exposed to high-pressure steam, the whole operation of cleaning and sterilization occupying about 15 minutes. Equipment of each of these types is described by Perkins (1956)

STERILIZATION BY DRY HEAT

Just as autoclaving is the only feasible method of sterilizing fabrics, watery solutions and rubber, so is exposure to hot air the only method applicable to oils (including Vaseline) and most powders. These are not penetrated by steam, and since dry heat must be applied at a much higher temperature than steam, the temperature attained in an autoclave is inadequate. Dry heat is also a satisfactory method for metal instruments, and the best for glassware, including syringes.

Sterilization of syringes

Syringes deserve separate consideration. Chemical methods of sterilizing them are unsatisfactory (Memorandum, 1945) and boiling in water destroys only vegetative bacteria *Absolute sterilization is possible only by autoclaving or by the* use of dry heat, and of these the latter is much the better method. Steam does not penetrate, and therefore cannot sterilize, a lubricated syringe (Stewart, 1957); hence if this method is to be employed, a lubricant, whether silicone or oil, must be dispensed with. Apart from this difficulty, the syringe must be adequately exposed to steam, and therefore cannot be enclosed in a tube or other such container intended to protect it against contamination until it is used. Ludicrous examples of syringes packed in metal boxes or enclosed in tightly plugged tubes even sealed with adhesive tape before being autoclaved have recently been described and illustrated (Report, 1958). In such conditions access by steam, particularly of the interior of a syringe, *must be almost entirely prevented. On the other hand, dry* heat, properly applied, is certain in its action and is suitable for syringes completely sealed in metal containers in which they can remain until needed for use. A syringe service operating in this way for a whole hospital, or group of hospitals, is the best solution of this problem.

Time-temperature relationships

The usually accepted conditions for sterilization by dry heat are exposure to 160°C. for 1 hour, although that prescribed in the *British Pharmaceutical Codex* is only 150°C. for the same period. This rule can now be amplified on the basis of ingenious and exhaustive tests recently conducted by *Darmady, Hughes and Jones* [illegible]
[illegible]
[illegible]
statically controlled hot-plate. This apparatus permitted exceptionally exact control

of temperature, and the time taken to reach the desired temperature was also accurately determined. On the basis of their results, these authors recommended the times of exposure to different temperatures given in Table III, these times allow

TABLE III

TIMES RECOMMENDED FOR DRY HEAT STERILIZATION*

Temperature (°C.)	*Holding time recommended* (*minutes*)	*Colour change, Browne's tube No 3* (*minutes*)
150	—	91
160	45	51
170	18	26
180	7½	17
190	1½	7

* Darmady, Hughes and Jones (1958) (These times do not include that required to raise the load to the temperature stated)

a considerable margin of safety. It will also be observed that the Browne tube behaves correspondingly except at the two highest temperatures.

Hot-air ovens

These appear to stand as much in need of reform as autoclaves. Many are still in use which have no fans to maintain air circulation, and without these hot air naturally layers over cooler, with the result that temperature in different parts of the chamber may vary by as much as 40°C (Ewald and Schmidt, 1953, Darmady and Brock, 1954).

It is imperative that the air be kept in motion, and free passage must also be allowed for it between items in the load If boxes or other containers are closely packed together, the time taken to reach the necessary temperature is unduly and dangerously prolonged An alternative to the usual type of oven, in which the heating elements are in the walls, is the German "Rotasteril" (Oesterle and Hertwig, 1957), an insulated chamber with an outlet and inlet for air which is heated by passage through tubes containing heating coils. This system is said to enable the desired temperature to be attained rapidly and maintained with a high degree of uniformity throughout the chamber.

Other methods of applying dry heat

Two other systems deserve mention, one for the very large and one for the small user In a large syringe service the most rapid turnover can be attained by passing syringes sealed in metal containers on a conveyer belt through an insulated chamber in which they are exposed to infra-red radiation, producing in them a temperature of 180°C or more for about 10 minutes of the 22-minute run (Darmady, Hughes and Tuke, 1957)

For the small user, such as an individual practitioner, the insulated aluminium block bored with holes to accommodate syringes used in the experiments of Darmady, Hughes and Jones (1958) should serve very well. Placed on a

thermostatically controlled hot-plate, it attains a high temperature in a short time. In addition to sterilizing syringes, it can be fitted with a tray to accommodate small instruments (Darmady, Hughes, Jones and Tuke, 1958).

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ABSTRACTS RELATING TO STERILIZATION BY HEAT

Sterilizers

Bowie (1958a) emphasizes the dangers which may result from bacterial infection acquired in hospital. For instance, staphylococcal infection may produce alarming results among new-born babies in overcrowded maternity hospitals. This type of infection is [illegible] hospitals are inadequately staffed, designed or equipped. With regard to [illegible] for the correct design, installation and [illegible] is to be purchased for use in a surgical [illegible]

includes not only the various high prevacuum machines but also pressure cookers and hot-air ovens To operate a manually controlled gravity-displacement machine is by no means a simple matter, for it may be necessary to carry out no fewer than 39 stop-valve manipulations during each sterilization run. Full automatic control has become common practice in America and on the Continent, where the saving in nurse hours has proved

Automatically controlled, high pre-vacuum sterilizer

Discussing modern sterilizers, Bowie (1958b) states that the machines manufactured in Germany are under full automatic control and have effective water-sealed electrical centrifugal vacuum pumps German manufacturers specialize in the production of

The process of sterilization consists of 7 stages. Air is extracted to a chamber negative

ing to the nature of the load. Autoclaves of this type cannot be used for bottled fluids and should be labelled accordingly

Testing of sterilizers

Kelsey (1958) discusses the testing of sterilizers. A survey has been made of the heat resistance of various spore preparations at present used for testing. A series of 25 preparations was tested by heating for various times at 100°, 110° and 121°C. The tests at 100°C. were made in a steamer, using piped steam; those at 110° and 121°C. were made in a domestic pressure cooker modified to receive steam under pressure from a laboratory autoclave

at 37°C fo

unheated sp

possibility

envelop, at least one negative culture of each preparation was inoculated with a second

and unheated spore "paper" and in each of these growth took place overnight. The results showed that none of the preparations tested approached a satisfactory level of heat resistance. In testing the efficiency of a sterilizing process, two methods are available. [illegible]

[illegible] hospital sterilizers may appear revolutionary, a parallel is provided by the testing of milk for adequate pasteurization.

Thermal death-times of spores in dry heat

[illegible] ments [illegible] nade, [illegible] *ther-* [illegible] -rmo- [illegible] late; the temperatures were ascertained by means of thermocouples; holes had been bored in the long axis of the block to take syringe-containers. The results were as follow: (1) dried [illegible]

[illegible] *mophilus*—at 150°C. no growth was obtained after 8 minutes. These results agree with [illegible]

[illegible] Browne's tube No. 3 provides an adequate guide to safety except perhaps at temperatures above 170°C. In the comparison with Browne's tube, the shortest time taken to change colour was regarded as the critical period and any time in excess of this can be considered to be an excess safety margin.

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PEPTIC ULCER OF THE STOMACH AND DUODENUM*

A review of its pathogenesis in relation to surgical treatment

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As befits a common disease which is still increasing in frequency—and possibly in severity also—peptic ulceration continues to engage the interest and the energy of a host of clinical and laboratory investigators; in consequence, although there have been no striking discoveries in respect of aetiology or fundamental developments in respect of management, there has been a steady and significant accumulation of knowledge on many aspects of the disease. Thus we are now relatively well informed about the quantitative and qualitative features of the gastric secretion, about the behaviour of the stomach in response to various stimuli and about the role of the gastric antrum and the functions of the vagus nerves A new field of pathology has been revealed with the discovery of the blood group associations of peptic ulcer, and of the relationship of certain states of endocrine over-activity to [illegible]
results of [illegible]

As a co [illegible]
of peptic ulcer with more circumspection than ever before Furthermore, the issues that arise in respect of the management of the more common complications are now defined with sufficient sharpness to justify almost dogmatic solution.

The purpose of this review is to scrutinize briefly the more recent contributions to our knowledge of peptic ulcer disease as it affects the stomach and duodenum and to consider their possible significance on clinical strategy and tactics.

AETIOLOGY

The precise aetiology of gastroduodenal ulceration is still not known; and indeed it is probable that not all ulcers have a common aetiology. Nevertheless, many of the general circumstances in which ulceration occurs are now appreciated, and

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the local factors concerned in the pathogenesis of the ulcer lesion are clearly recognized.

PATHOGENESIS

The starting point in any study of the pathogenesis of peptic ulceration must always be the presence of acid and pepsin, because peptic ulcers are found only in situations to which acid and pepsin naturally or artificially have access. These sites are the lower end of the oesophagus, the stomach, the duodenum, the jejunum when anastomosed to the stomach, and the ileum at its junction with a Meckel's diverticulum which is lined in whole or in part with gastric mucosa. However, since nearly all stomachs secrete acid and pepsin but only a small number become ulcerated, we have to postulate some "factor" in the mucosa which normally resists digestion. It is the outcome of this play of forces—mucosal resistance versus acid peptic digestion—that determines whether or not an ulcer forms; and the relative importance of these two main factors differs in different ulcers. We may imagine, for example, such a high and continuous acid secretion that it alone is sufficient reason for the formation of an ulcer; conversely we may imagine a mucosa which is so degenerate that it is readily damaged by traces only of acid peptic juice. We believe that there is a gradient of mucosal vulnerability, and that the jejunal or oesophageal mucosa ulcerates more readily than that of the stomach. But whatever factors are relevant they can act only on one or other side of the central equation, acid pepsin or mucosal resistance.

There are good surgical grounds for regarding duodenal and gastric ulcers as separate and distinct clinical problems. It has even been claimed that they may well be different diseases, with different aetiological factors, but this view is not supported by pathological observation of the ulcer lesion; and though a different therapeutic approach to each type is probably justified, the ultimate mechanism of ulceration is identical in both situations.

Factors in acid-pepsin secretion

In whatever way we choose to stimulate a series of stomachs, we get different responses. To explain these differences in secretory response, we can postulate three main factors or variables: (1) the secretory cell mass, that is, the actual population of functioning secreting cells, (2) the stimuli, whether nervous or hormonal, which act on these cells; and (3) the mechanism of inhibition of secretion.

(1) *The secretory cell mass*

The concept that the amount of hydrochloric acid secreted by the stomach is conditioned by the number of functioning cells present, the "secretory cell mass", is so obvious that it is difficult to credit how it escaped recognition for so long. Nevertheless, a study of the literature on test meals shows that the secretion of acid was generally reported in terms of concentration, and this confusion persists. If we contemplate only the acid output of a parietal cell and we suppose that the output of each cell is the same, the concept of a population of cells, each contributing its moiety of acid, becomes irresistible. How concentrations vary from one stomach to another, or in one stomach at different phases of secretion, is a

subject for argument; there are two main theories. One theory suggests that there is a constant primary concentration of acid which is diluted by an alkaline non-parietal cell secretion, so that the larger the output of acid the higher will be its concentration. The other theory affirms that, since there is always a tendency for hydrogen ions to diffuse back into the cell, there to be exchanged with sodium ions, the concentration of acid will be related to its rate of secretion; the higher the rate, the higher the concentration.

Guiss and Stewart (1948) showed that there was a significant relation between parietal cell counts and the highest concentration of acid reached in a previous test meal, but a mathematical analysis of the relationship between the cell population and the output of acid was first attempted by Adam and his colleagues (1954). These workers gave a series of infusions of histamine of different strengths to human volunteers and related the output of acid to the infused dose. They analysed the resulting sigmoid curve and suggested that, of the three parameters which determined the curve, the most important in defining the secretory response to histamine was the one relating to the secretory cell mass On this theory, the maximal limiting acid output of the stomach should be directly related to the number of parietal cells present

Observations to confirm this theory were carried out by Card and Marks (1959) on human subjects, and an excellent correlation between the "maximal" output of acid and the parietal cell mass was obtained This correlation was confirmed in dogs by Marks, Komarov and Shay (1958). There is thus a firm basis for the concept that the limiting output of hydrochloric acid from the stomach is directly related to the number of cells present.

(2) *The secretory stimuli*

Certain biochemical conditions are necessary for the formation of hydrochloric acid from the parietal cells; for example, an adequate blood flow is essential for the carriage of carbon dioxide to the cell, and for the carriage of oxygen and glucose for energy purposes Other biochemical substances may also have to be present—for example hormones, about whose function we know little. These substances are not usually regarded as stimuli but as having a permissive role, in the sense that in their absence secretion does not occur. Though it is possible in the animal to depress the secretion of acid by forced respiration so that carbon dioxide is washed out of the blood, we do not normally regard carbon dioxide as a stimulant of acid secretion

The stimuli proper are nervous and hormonal It has long been recognized that the vagus was the secretory nerve to the stomach and that the earliest or cephalic phase of secretion was entirely vagal in origin. There is no doubt also that there is a hormonal phase of secretion mediated through gastrin released in the antrum. The occurrence of secretion in a transplanted pouch when the antrum is stimulated by distension can hardly be explained in any other way Additional evidence is supplied by the injection of histamine-free extracts of the antral mucosa which stimulate gastric secretion

The cephalic and the hormonal phases of secretion used to be regarded as distinct and separate entities, but there is now no doubt that in fact they are intimately related. Gastrin is released after vagal stimulation, by distension of the

antrum or by peristalsis, and also by the introduction of food extracts (Oberhelman, Rigler and Dragstedt, 1957; Woodward and his colleagues, 1957). By the use of a hybrid antrum (Baugh and his colleagues, 1957), it has been shown that the muscularis layer is not the site of gastrin formation. In fact the cells of origin are unknown, though it has been suggested that it is released from Meissner's plexus or other nervous structures in the antrum. Investigation of the gastrin mechanism can be carried out experimentally in animals, in which it is possible to use a denervated Heidenhain pouch as an "indicator" in association with various types of antral pouch. It should be noted that gastrin is a stimulant only of acid, and one may speculate on the existence of another hormone, yet to be discovered, which would stimulate the secretion of pepsin. Such a "gastrozymin" would be analogous to the pancreozymin which stimulates the secretion of pancreatic ferments.

(3) *The mechanism of inhibition*

Not only must there be a mechanism for starting the secretion of gastric juice, but equally also there must be a mechanism for stopping it. In patients with duodenal ulcer, the fasting secretion is frequently high and this continuous secretion might conceivably be due to a failure in the inhibitory mechanism. "Inhibition" might be the result of cessation of the stimuli causing secretion, or it might be a more positive process such as the release of an inhibitory hormone.

It is clear from a number of experiments that acid introduced into the antrum either prevents the release of any further gastrin or, more speculatively, releases an actual inhibitory hormone. In animals in whom the antrum is isolated from the main stomach but left innervated, it can exert its action as a stimulant of gastric secretion, but, because acid no longer gains access to it, the secretion of gastrin continues unhindered. This produces an augmentation of the 24-hourly secretion, and a spontaneous secretion which is normally absent in the dog (Brackney, Campbell and Wangensteen, 1954). Andersson, Elwin and Uvnäs (1958) showed that the response to insulin hypoglycaemia was elevated and this was interpreted as an effect of the vagus on the antrum. These increased responses diminished after antrectomy. The production of two separate antral pouches, with an "indicator" Heidenhain pouch, allows stimulation of one antral pouch with liver extracts, while an inhibitory effect can be produced by the introduction of acid into the other. Though the existence of an active inhibitor cannot yet be regarded as proven, the effectiveness of acid on the antral mucosa in stopping further acid secretion is undoubted (Jordan and Sand, 1957; Longhi and his colleagues, 1957).

The mechanism for the inhibition of acid is not confined to the antrum, for there is also one which operates from the duodenum. Sircus (1958) summarized the literature on this subject and showed in dogs that there were at least two types of mechanism, one sensitive to changes in *p*H, the other to changes in osmolarity. The *p*H-sensitive mechanism appeared to utilize a nervous pathway, while the osmolar-sensitive mechanism operated through a humoral pathway. The antrum played no part in these activities. Such a mechanism implies nerve endings sensitive to changes in *p*H, and Iggo (1957) has clearly demonstrated the existence of such endings in the gastric mucosa.

In man, it is impossible to disentangle all the factors that influence gastric

secretion as readily as may be done in animals We do not even know if all the mechanisms are the same though, as a working hypothesis, we may assume that they are. Even if the mechanisms are similar to those in animals, we do not know if they have the same relative importance

Variations in gastric secretion

Examination of the acid secretion in normal persons and in subjects with peptic ulcer, using the maximal histamine test, shows that there is a wide range of outputs. If we accept the evidence that the response is an expression of the size of the parietal cell mass, this means that there are wide variations in parietal cell masses, and such differences will go far to explain the different secretory performances of different stomachs.

It is clear from the therapeutic effects of vagotomy that the vagus plays an extremely important part in human gastric secretion. How far, therefore, can different responses be ascribed to differences in vagal activity? The fact that basal secretion, which is sometimes very high in patients with duodenal ulcer, is largely reduced by vagotomy has been used by Dragstedt (1956) as an argument that the greater secretion of acid in these patients is nervous in origin and is due to hyperactivity of the vagus. This reasoning fails to distinguish the two variables which are involved, namely, the parietal cell mass and the vagal tone. It would appear that the greater basal secretion may well be explained simply by a greater cell mass (Hunt and Kay, 1954) without invoking a hypothesis of vagal hyperactivity This conclusion does not detract from the usefulness of vagotomy as a method of reducing a high secretion.

The part played by the antrum in gastric secretion in man is not easy to assess; we get some idea of its importance, and of the associated acid-inhibitory mechanism, in considering the effects produced when the antrum is retained but excluded from continuity with the main body of the stomach Under these conditions, the gastrin mechanism should be operative, and the acid secreted cannot now inhibit the further release of gastrin The results of such operations are most instructive and show how disastrous is the absence of the "acid brake" (Bales and Schilling, 1956) Such observations form a close parallel to the results of similar

of any alteration of the inhibitory mechanism in the ulcer group.

To summarize the position in man, it seems that increase in the secretion of acid either as fasting secretion or in response to stimuli is mainly caused by an increase in the number of cells, and that we have as yet no evidence for any increase in the activity either of the vagus or of the gastrin mechanism. Nor is there evidence for a failure in the processes of inhibition. Gastric secretion can be reduced surgically by removing part of the parietal cell mass, or by interrupting the stimuli which act on the parietal cells, that is by cutting the vagal nerves and by removing the antrum All these methods are soundly based and effective; the selection of a particular one must depend on such other considerations as permanency of effect, operative hazard, and untoward post-operative sequelae; these aspects of the surgical treatment of peptic ulcer are considered later

Mucosal resistance

Local factors

Diminished mucosal resistance as a factor in the genesis of peptic ulceration has been less well studied than the gastric secretion, as it is less amenable to investigative methods Nevertheless, the evidence that it is of considerable significance, though largely circumstantial, is very suggestive. Thus, not all hypersecreting stomachs become ulcerated; and duodenal ulcers sometimes arise in those with normal gastric secretory activity, while gastric ulcer is more often than not associated with a normal or low acid output. Furthermore, even in the grossest hypersecretors, gastroduodenal ulcer is not a diffuse mucosal lesion but strictly circumscribed to well-defined areas and of an extent that is remarkably constant. These observations suggest that not infrequently factors other than pepsin and hydrochloric acid must be concerned in the production of ulcer, and occasionally *may prove to be even more important than the gastric secretion.*

Mucosal resistance may be the result of several properties—the presence of the mucus barrier, the inherent "health" of the gastric epithelium and its capacity for complete and rapid regeneration, and its lavish blood supply.

Ever since the work of John Hunter in the eighteenth century, and of Harley in the last century, the superficial layer of mucus and the mucus-secreting cells have attracted attention as the probable first lines of defence in the stomach. The latest proponent of this view, Hollander (1954), has shown how very rapidly the mucus cell layer can regenerate when it is damaged, and we must assume that the *mucus cells in the stomach are continually being shed,* a process with which regeneration normally keeps pace.

There is some evidence, of a different kind, of an additional specific resistance to gastric digestion of the mucosa. Barrett (1956) showed that the normal glandular mucosa in one strain of rat is resistant to its own secretion, but is vulnerable to the secretion of a different rat. Possibly a breakdown in this mechanism could lead to ulceration, and the idea recalls the general concept of auto-immunity as manifested, for example, in the chronic thyroiditis of Hashimoto.

It is obvious that the inherent vitality of the gastric epithelium must have a considerable influence on its resistance to digestion. There is some evidence that the health of the gastric mucosa is under hormonal control and that, in animals (Baker and Abrams, 1954) and probably also in man, the absence of the pituitary results in degeneration of the mucosa, though this has no practical significance in the average case of ulcer The other factors concerned in the preservation of epithelial health are obscure, but it is quite certain that local changes may undermine it

Thus it is now well recognized that in persons with gastric ulcer the mucous membrane of the stomach is almost invariably abnormal and sometimes grossly so. The histological change *has been loosely defined as chronic and atrophic gastritis;* it is accompanied by a reduction in the population of parietal cells; and the atrophy is confined to or most marked in the territory of the pyloric glands, and peptic ulcer is sited outside it only when the "gastritis" is severe and diffuse. The junction between the acid-producing mucosa and that carrying the pyloric glands is very variable, but often lies a considerable distance proximal to the incisura which by

anatomical convention is said to mark the boundary between the two territories. Card and Sircus (1958) have recorded that around gastric ulcers there is a spreading zonal gastritis that may extend even into the acid-producing mucosa. Though not proven, it is likely that the gastritis is a sequel to the ulcer; and a similarly induced gastritis as a consequence of long-standing duodenal ulceration with hypersecretion might well explain the subsequent occurrence of gastric ulcer many years after the duodenal lesion has become quiescent, it may explain also the hyposecretion, since the functional ability of the acid-producing cells would be depressed. The proportion of gastric ulcers that follow in the wake of duodenal ulceration is variously stated, but is probably in the neighbourhood of 25 per cent (Johnson, 1947).

The cause of pre-ulcer gastritis in persons who develop gastric ulcer without a previous duodenal ulcer is not known; but since we have no means of knowing their secretory status before the gastric lesion appears, it is possible that hypersecretion to a degree insufficient to induce duodenal ulcer has been the gastritis-producing factor. Johnson (1947) suggested that stasis might lead to gastritis, and Dragstedt (1956) also favoured gastric retention as an explanation, but since delayed emptying is by no means invariable in gastric ulcer, it is difficult to see how this can explain all cases

General factors

It is possible that the gastric mucosa may be made "sick" not by locally-acting insults, but by general factors; and indeed this may account for some of the curious features of the incidence of ulcer-disease So far a satisfactory explanation has not been advanced for the curious geographical and racial distribution of peptic ulcer but since racial and climatic differences in acid-pepsin secretion have not been observed, it seems probable that whatever factors are operative, they act by affecting the mucosal defence.

It is tempting to suppose that of the possible environmental factors, diet is the most important. It could influence the stomach in two ways—by containing a substance or substances directly hostile to the stomach mucous membrane, or by lacking something which is essential for the inherent quality of the mucosal cells. The occurrence of gastric ulcer in states of advanced malnutrition is well recognized; for example, the incidence was high among the grossly undernourished population of the Japanese prisoner-of-war camps, and Somervell (1942) attributed the great prevalence of duodenal ulcer in South India to the same cause. In Great Britain the incidence of fatal peptic ulcer, and especially of gastric ulcer, is higher in the lower social strata; but so many factors in addition to nutrition operate in these circumstances that it is unsafe to draw any conclusions. Certainly the experimental induction of nutritional disturbance has failed to reproduce peptic ulceration.

Vascular considerations

Interest in the gastric blood supply and in the relation of vascular lesions to peptic ulceration is of long standing The concept that acute ischaemia caused necrosis of a segment of the gastroduodenal mucosa which was then vulnerable to the action of the gastric juices depended on Disse's (1909) claim that the mucosal

arteries were end-arteries, and numberless theories were advanced to explain the vascular occlusion.

It is now clear, however, that the mucosal and submucosal vessels are not end-arteries, they anastomose freely with each other; and in addition there are numerous arteriovenous communications (Barlow, Bentley and Walder, 1951). The latter are probably under autonomic nervous control and serve to "shunt" blood to and from the mucous membrane in response to varying phases in gastric physiology. The colour changes seen in the mucous membrane during gastroscopy and at operation are presumably the result of alterations in mucosal blood flow dictated by fluctuations in the activity of the "shunts"; and it is possible that prolonged deflection of blood from a segment of mucosa as a result of the continued operation of the shunt mechanism may produce an area of total mucosal ischaemia and, later, ulceration. Blood flow through the arteriovenous channels is increased and sustained by epinephrine (Walder, 1952), one of the substances used in the experimental induction of ulcer in the animal laboratory.

Studies by micro-angiography of the blood vessels of chronic gastric ulcers (Key, 1950) show that there is an avascular zone around the ulcer; this may extend through the whole thickness of the stomach wall and also some way along the lesser curvature. Despite the extensive occlusion of the deeper vessels, the mucosal arteries are well filled up to the edge of the ulcer, suggesting that an ischaemic lesion in the deeper tissues has preceded the mucosal breach. It may be that the occlusion of the arteries round the ulcer is the result of chronic inflammation secondary to the ulceration. Certainly this affords an explanation for lack of healing, and even for a tendency for the ulcer to increase in size.

The vascular state of an acute ulcer is very different, here there is marked increase in vascularity not only in the mucous but in the submucous zone as well. There is both clinical and experimental evidence that vascular engorgement, with capillary dilation and possibly stasis may lead to ulceration. Wolf and Wolff (1947) reported that in Tom, their patient with a gastric fistula, acute emotional upset caused engorgement and swelling of the mucosa and eventually small erosions that bled freely; and histamine has a similar effect.

Whether and how such acute lesions are related to chronic peptic ulcer is not clear. The acute lesions are shallow and multiple, often situated away from the recognized "ulcer areas", and it may be that they represent a different form of peptic ulceration. Such a mechanism may explain the ulcers that occur in lesions of the hypothalamus and other parts of the brain.

In summary, there is good evidence that diminished resistance on the part of the gastroduodenal mucosa can lead to acute mucosal erosions and ulceration. Such lesions have their own clinical importance as a cause of bleeding which is sometimes severe enough to demand operation, but their relation to the chronic ulcer of human pathology is not clear, and a solution to this problem must await further information.

Sex and the incidence of peptic ulcer

One of the striking features of peptic ulcer is the sex difference in incidence and clinical course. The disease is always less common in women, thus, gastric ulcer is three or four times, and duodenal ulcer ten times less frequent than in men.

In women too, the natural course of the ulcer is milder, so that perforation and haemorrhage are less common, especially during pregnancy, though at rare intervals such incidents do occur (Vasicka, Lin and Bright, 1957, Finley and Finley, 1957). Anastomotic ulcers are likewise rare after operative treatment of any kind.

Ulcers seldom originate or flare up during pregnancy, indeed, symptoms and signs of activity frequently disappear (Clark, 1953) The cause of this apparent immunity is unknown, and there have been some investigations to determine if gastric function alters during pregnancy.

In dogs, there is evidence that the secretion of acid does not increase during pregnancy (McCarthy, Evans and Dragstedt, 1954). Studies of gastric function in some pregnant women by Hunt and Murray (1958) did not yield evidence of any increase in secretion, but rather a fall which was at its lowest about the thirtieth week of pregnancy. As in animals, lactation was associated with a significant increase in gastric secretion which did not occur in patients who were not breast-feeding their babies

The general conclusions are that acute ulcers or acute exacerbations of ulcer are rare during pregnancy, though we do not know if chronic ulcers heal or merely become quiescent; and that there is no striking change in gastric function to account for these findings.

Peptic ulcer complicating major surgery and injury

An association between peptic ulcer and severe injury has been recognized since Curling (1842) recorded 11 examples following burns; and between peptic ulcer and operation since Billroth (1867) reported a patient who died from haematemesis 6 days after the removal of a retrosternal goitre It is now appreciated that no brand of severe accidental injury is immune; and though peptic ulcer has apparently complicated a comprehensive range of surgical operations, urological and intra-abdominal procedures appear to be particularly liable to such a development From the clinical point of view, the association is an important one to recognize, since the ulcer may present acutely with haemorrhage or perforation, complications that may be potentially more dangerous than the original condition, and are in fact often lethal

Apart from trauma and operation, acute and often fatal gastroduodenal ulceration may complicate such medical emergencies as coronary thrombosis (Mears, 1953), cerebrovascular accidents (Fletcher and Harkins, 1954) and chronic so-called "stress" diseases such as ulcerative colitis and hypertension

The ulcer may be a new acute lesion or a recrudescence of a healed or chronic ulcer, or there may be several ulcers Either the stomach or the duodenum, or both, may be affected, and haemorrhage may occur from more than one lesion simultaneously

The aetiology of these ulcers is not clearly established, though the ultimate mechanism in their production must, as always, be either a change in gastric secretion or in mucosal resistance. An opportunity seldom presents to investigate the gastric secretion in "stress" ulcer, but there is some evidence that it is increased. Hummel, Lanchantin and Artz (1957) investigated 26 burned patients, and found that gastric acidity was raised in almost all patients with burns involving 35 per cent

or more of the body surface, and that it tended to be higher in the more seriously burned. However, the level was of little value in predicting the appearance of an acute ulcer.

There are several ways in which such gastric abnormalities may be brought about. The prevailing fashion is to group them as "stress" phenomena, but stress is a confusing term in this context. It stems from the concept that in some way peptic ulcer is one of the penalties paid for the strains, the worries, the anxiety and the speed of modern existence; and it derived some support from the tendency of ulcer symptoms to begin or reappear during periods of emotional disturbance.

It is tempting to seek for a nervous pathway by which such tensions could affect the stomach; and the occurrence of similar acute ulcers in diseases of the central nervous system, and especially the hypothalamus (Rokitansky, 1846; Cushing, 1932) seemed to bridge a gap between hypothesis and actuality. Porter, Movius and French (1953) demonstrated that gastric hypersecretion following injury or stimulation of the anterior hypothalamus was prevented by vagotomy; and it seems likely that an increase of vagal tone may be one mechanism for hypersecretion and ulcer in circumstances associated with emotional strains, fears and anxieties.

The view that injury and disease evoked a pattern of body response with aspects other than nervous was first propounded by Selye (1950). Important amongst such responses were those of the adrenal cortex, and the occurrence of peptic ulceration in patients under treatment with the adrenal steroids suggested another possible mechanism Gray, Ramsey and Thorn (1956) suggested that in "stress", the cells of the anterior hypothalamus secrete a humoral substance that stimulates the anterior pituitary to release corticotrophin, the consequent secretion of cortisone by the adrenal cortex causes increased secretion by the stomach. This simple and attractive explanation lays most of the blame for "stress ulceration" on cortisone; but in effect the problem is less simple than such theorisings would have us believe, for the role of the adrenal steroids in gastric physiology is a complicated one.

Relation of cortisone and corticotrophin to peptic ulcer

The advent of the corticosteroid drugs has stimulated a great deal of interest in the relationship of the adrenal hormones to gastric function and to the pathogenesis of peptic ulcer Many of the experimental results are conflicting, and it is only possible to summarize what is probably the present position.

(1) There seems general agreement that the giving of cortisone and corticotrophin carries the risk of producing an ulcer or of reactivating an old one (Sandweiss, 1954) Treated with ordinary conservative measures such ulcers have been shown to heal if steroid administration is stopped, and also if it is continued (Brush and his colleagues, 1957).

(2) In Addison's disease, it is generally conceded that peptic ulcer is very rare or unknown. Now that replacement therapy is possible, ulcers have appeared during the course of treatment (Gray, Ramsey and Thorn, 1956; Engel, 1956)

(3) An obvious experiment is to test the effect of these drugs on gastric secretion, and this has been done in dogs and in man In adrenalectomized dogs, it has been clearly shown that replacement by cortisone produces a secretion equivalent to

that obtaining before adrenalectomy, and one that shows some relation to the dose given (Sigel, Bassett and Cooper, 1957). In normal dogs, some workers have failed to demonstrate any response to cortisone (Ragins and his colleagues, 1956) In human beings, Gray (1957) reported an increase in secretion in some of those tested, but other workers have failed to confirm these findings. Using the "maximal" histamine test Crean (1959) found increased response to cortisone in some patients. It may be that only a small proportion of people respond in this way, a finding that in itself is one of great interest. There seems no doubt from the careful work of Hirschowitz and his colleagues (1956), however, that the occurrence of a peptic ulcer in a subject taking cortisone is not necessarily preceded by an increase in gastric secretion of acid and pepsin.

A further step in the investigation of this problem is to see if peptic ulcer patients can be shown to have any abnormal hormonal responses to corticotrophin. Cummins and Gompertz (1957) investigated the plasma levels of total 17-hydroxy-corticoids following stimulation in a group of non-ulcer patients and a group with active duodenal ulcer. There were no significant differences, and though the study did not exclude an adrenal cortical mechanism in the pathogenesis of peptic ulcer, it did not support the concept of cortical hyperactivity as a direct aetiological agent.

It might be that the ulceration observed with these drugs does not arise through any special aetiological mechanism, but primarily from a difficulty in healing. This has been the subject of a careful study by Janowitz and his colleagues (1958), who made experimental ulcers in gastric explants in dogs and inspected them daily. There appeared to be no delay in resurfacing the superficial layer, but healing itself was retarded. They concluded that these drugs might aggravate ulcer in man by their effect on healing, apart from any effect on secretory activity.

The present position may be summed up by saying that the adrenal cortex exerts a permissive effect on gastric secretion; that in its absence gastric secretion is minimal; that in large doses, in some instances, it can increase the gastric secretory response; that cortisone-induced ulceration in human beings is not necessarily preceded by this increase in secretion; and that, as part of its action, cortisone may interfere with gastric healing.

Blood groups and peptic ulcer

Clinicians have long sought to convince themselves, and others, that there is a particular type of individual who is prone to develop peptic ulcer, who can be recognized by build, demeanour, and expression; and both physician and surgeon have been glad to fall back on the concept of an "ulcer diathesis" as an explanation for their therapeutic failures Both of these cherished beliefs can be disputed on the grounds on which they are advanced, but the discovery by Aird and his colleagues (1954) of an association between blood groups and peptic ulcer is scientific evidence that genetic "make-up" is of considerable importance in peptic ulceration and other gastro-intestinal diseases The fact is that in patients with peptic ulcer there is a higher proportion of persons with blood group O than amongst the general population The difference is more marked in duodenal than in gastric ulceration, but in both the relationship is statistically significant. Aird's original observations have now been confirmed from many sources and from

many countries; and from the study of a large number of cases it is possible to state in mathematical terms that persons with the O blood group have a 38 per cent greater chance of developing a gastric ulcer than those of other blood groups.

The blood group substances A, B and H (corresponding to the blood groups A, B and O respectively) are mucopolysaccharides distinguished the one from the other by their differing antigenic properties. In most people they are secreted in the fluids of the digestive tract, in greatest concentration in saliva and in the gastric juice. At first sight it is reasonable to suppose that the blood group substances A and B must bestow increased local protection against peptic ulcer and that the O substance, H, must be less effective. Some point was given to this argument by the observations of Wallace and his colleagues (1958) that the incidence of group O individuals was highest in the group with the severer forms of ulceration, and especially in stomal ulcers after gastro-enterostomy and gastrectomy.

A number of individuals do not secrete the blood group antigens in their digestive secretions; and Clarke (1955) showed that amongst patients with duodenal ulcer there was a significantly greater proportion of non-secretors than amongst normal subjects. This was to be expected if the theory of a local protective action of the blood group substances was true, but the proportion of non-secretors with peptic ulcer belonging to group O was about the same as that in secretors. In view of this it appears that the greater susceptibility to ulcer of group O individuals does not entirely depend on a local protective action.

The mechanism of a direct effect of the blood group on the occurrence of, or the protection from, ulcer is at the moment obscure. There does not appear to be a greater tendency to ulcer amongst siblings with group O than with group A, and since this finding is geographically uniform, it is unlikely that selective in-breeding is responsible. It has been suggested that liability to ulcer in group O subjects is an immunological matter, though as Aird has suggested, the protective influence may be exerted not through the gastric mucus, but directly by the presence of the group substances in the mucosal cells. It is also possible that in some way the differing blood groups are genetically associated with variations in gastric secretion.

There are obviously many other facets of this intriguing relationship to be scrutinized. At the moment, the most that can be said dogmatically is that there is a predominance of group O individuals amongst patients with duodenal ulcer; and a predominance of non-secretors; and that the significant excess of non-secretors in the group with severe ulceration and in those coming to operation may provide a prognostic test, in so far as the absence of the secretion of blood group substances may indicate the desirability of surgical treatment. In the long term, the benefits of the discovery should be considerable, since increased understanding will throw light on the aetiology—and possibly the prevention—of peptic ulceration

Peptic ulcer and the pancreas

The association of severe, intractable, progressive and even lethal peptic ulceration with non-insulin-secreting tumours of the pancreatic islets was first noted by

Ström (1953) and confirmed later by Zollinger and Ellison (1955). The number of cases now recorded runs to more than 100 and there is no doubt that the Ström-Zollinger-Ellison syndrome is now established as a clinical entity. The peptic ulcer, which may occur in any one or more than one of the usual sites, or even in the upper jejunum, is accompanied by intense gastric hypersecretion which persists despite surgical treatment adequate for the usual forms of ulceration. This suggests that whatever the ulcerogenic mechanism, it must act directly on the acid-pepsin-producing cells, and not by way of the nervous or hormonal stimuli of gastric secretion.

The possibility that the pancreatic tumour was the cause of the ulceration has aroused fresh interest in the role of the pancreas in gastric function. It is well known that deflection of the alkaline external pancreatic secretion from the duodenum leads to duodenal ulcer (Elman and Hartmann, 1931; Dragstedt, 1942); but the part normally played by the internal secretions of the pancreas is more difficult to define categorically. Insulin-induced hypoglycaemia is a stimulant of gastric secretion, acting by way of the vagal nerves; in fact this is the basis of the standard test for the completeness of surgical vagotomy. Poth and his co-workers (1950) found that continuous hypoglycaemia induced by commercial insulin caused peptic ulcer both in normal dogs and in those which had been subjected to pancreatectomy; since there was no correlation between the degree of hypoglycaemia and the occurrence of the ulcers, these workers suggested that the cause of the ulceration might be glucagon, a hyperglycaemic-glycogenolytic substance secreted by the non-*beta* (*alpha*) cells of the islets Zollinger and Ellison had identified by paper chromatography of the urine an abnormal protein with characters similar to those of glucagon: but Oberhelman, Rigler and Dragstedt (1957) and others have been unable to demonstrate hypersecretion or to cause ulcers by the administration of glucagon in healthy dogs

The *alpha*-cell tumours as a rule do not secrete insulin, and so the cause of the peptic ulcer is not hypoglycaemic excitation of gastric hypersecretion Furthermore, insulin-secreting (*beta*-cell) islet tumours do not cause peptic ulcer, though there are now on record a few cases of hypoglycaemia and peptic ulcer in association with mixed cell tumours of the islets and with a combination of *alpha*-cell and *beta*-cell tumours in the same glands

At the moment, the evidence for a causal relationship between the pancreatic tumour and gross gastric hypersecretion and peptic ulceration is slight Cure of the ulcer and reduction in the excessive gastric secretion by excision of the pancreatic growth has been achieved in one or two cases only; on the other hand, it is within the experience of most doctors that massive hypersecretion and gross and recurrent ulcer may occur in the absence of pancreatic tumour, and even after death from massive haemorrhage in such cases, the strictest search for pancreatic pathology has proved unavailing.

It has been suggested that in such cases there is hyperplasia of the non-*beta* cells of the islets rather than frank tumour (Summerskill, 1959); though such a change is a commonplace of endocrine pathology, it leaves unproved the problem of cause and effect in respect of the stomach lesions

So far nothing has been observed or discovered that excludes the possibility that

the gastric hypersecretion or ulceration and the pancreatic lesion or lesions are both due to the same external stimulant which may originate in one of the other endocrine glands.

Peptic ulcer and other endocrine glands

There is a clear association between hyperparathyroidism and peptic ulcer; indeed, an ulcer or ulcers may be the presenting feature either of a parathyroid adenoma or hyperplasia, though the cause for this association is unknown. Furthermore, peptic ulceration is commonly found along with multiple endocrine adenomas (Wermer, 1954) The simultaneous occurrence of such tumours—a kind of endocrine adenomatosis—is possibly not the pathological curiosity it was once supposed to be. The glands most commonly affected are the parathyroids, the anterior pituitary and the pancreas; but the pancreatic component—at least in overt form—is apparently not essential to the development of the peptic ulceration.

It is obvious that these recent observations have opened a new field of inquiry into the cause of peptic ulcer; at the moment, we can do little more than record and gather the facts, but in the next few years a careful study of the endocrine associations of peptic ulceration will obviously have to be undertaken.

At present the practical issues are hard to define. In the persistent ulcerators, the possibility of an endocrine lesion should be kept in mind, and exploration of the pancreas at laparotomy is an obvious step. It must be recalled that the tumours are not infrequently multiple and small, they may be ectopic—in the duodenal wall, for example (Oberhelman, Nelsen and Dragstedt, 1958)—and a high proportion have proved to be malignant, though the tempo of growth and dissemination may be slow.

There is general agreement that even when a pancreatic tumour is identified in a patient with atypical or recurrent ulceration, it is essential to combine appropriate treatment for the ulcer with removal of the tumour, or with pancreatectomy. This is obviously sound surgical practice, though it confuses the issue of cause and effect Indeed, in the published reports, successful treatment of the intractable peptic ulceration attributed to the pancreatic part of the operation appears to have been supplemented by the most radical gastric surgery. In this respect it is noteworthy that Zollinger and McPherson (1958) has suggested that on discovery of a pancreatic tumour the appropriate operation for the peptic ulcer is total gastrectomy, since small tumours or ectopic tumours may be left behind, and lead to disaster from fulminating recurrent ulceration in the post-operative period. Indeed, he went further, and recommended total gastrectomy combined with resection of the body and tail of the pancreas, whether or not a tumour is found, in patients who display the syndrome of severe and atypical peptic ulcer with gross hypersecretion. In the present state of knowledge, such a ruthless policy is hard to justify

Ulcer pain

In the past, much argument has raged round the cause of ulcer pain, and whether acidity or motility is the factor chiefly responsible. The protagonists of the acid theory of pain have sometimes been hard put to it to sustain their case. Woodward

and Schapiro (1954), investigating pain in the duodenum and its relation to *p*H and motility, produced pain in 4 out of 7 subjects when the *p*H of the duodenum was reduced below 1·88 by the intraduodenal administration of one-tenth normal acid, but only with amounts of acid that could hardly be called physiological—1·5 litres in one instance.

Very important observations were made by Wolf and Wolff (1947) in their subject, Tom, on the effect of various stimuli on the exposed gastric mucosa. They inflamed the mucosa with mustard oil, and thereby were able to show that its pain threshold was reduced; stimuli which were previously painless became painful, so that simple mechanical stimuli could produce intense pain. The importance of pain threshold and its alteration by inflammation recalls the views of Kinsella (1948). Analogous observations were made on the surface of the body years ago by Sir Thomas Lewis. The emphasis on pain threshold seems to be the most fruitful concept, and goes far to explain the opposing conclusions reached by different observers (Smith, 1955). It has received experimental support from the work of Iggo (1959), who was able to show that the threshold of "firing" in single nerve fibres could be lowered if the tissues surrounding the appropriate nerve endings were infiltrated with histamine or acetylcholine.

SOME PATHOLOGICAL CONSIDERATIONS

Key's (1950) demonstration of the dense fibrosis and almost complete avascularity surrounding a chronic gastric ulcer is enough to explain the difficulty of healing, and the difficulty of remaining healed. When the force of the ulcerating process has spent itself, the vascular mucosa may throw a pellicle of regenerated epithelium over the surface of the fibrotic base, but like the precarious epithelial cover of other chronic ulcers—as on the skin, for example—it is liable to disintegrate on the least injury. Thus, frequent relapses are an indication for surgical treatment on pathological as well as on clinical grounds.

To the pathologist, peptic ulcer in the stomach has been of absorbing interest since MacCarty and Broders (1914) reported that 68 per cent of all gastric ulcers were malignant or premalignant Although it did not take his brother pathologists and clinicians long to demonstrate the unsoundness of MacCarty's observations, it is still not uncommon to hear the possible transition of simple gastric ulcer to carcinoma advanced as an argument in favour of surgical treatment

Most surgeons who are interested in gastroduodenal work have seldom—if ever—encountered a true example of the translation. Indeed, it is not uncommon at operation to find a silent carcinoma of the stomach at a point remote from a simple ulcer, on the other hand, it sometimes happens that a lesion which appears simple clinically and radiologically turns out to be a primary ulcerating form of cancer Marshall (1953) at the Lahey Clinic found that 15·8 per cent of supposedly simple gastric ulcers were in fact malignant, and this figure—15 per cent—is the one usually quoted in the United States to represent this diagnostic error. In Great Britain the danger appears to be considerably less, especially if we exclude from consideration those patients in whom pre-operatively there is a strong suspicion, or even a presumption, of malignancy.

The position in Britain has been well summarized by Stewart (1955). Of 1,516

stomachs removed surgically, 103 showed carcinomatous ulcers, that is, under 10 per cent; but since a considerable number of gastric ulcers heal and are therefore not submitted to operation, the proportion of malignant to simple ulcers is much less. Thus, in a follow-up of "simple" ulcers for more than 3 years, Doll and his colleagues (1957) found only one example of carcinoma.

In the experience of Jordan (1958), neither *radiological appearance, situation,* or length of history are reliable criteria, although most clinicians are alerted by ulcers in the antrum, on the greater curve, or at the cardia. Despite its size the giant ulcer of the lesser curve is almost always benign.

DIAGNOSIS

Radiology

As a rule, the diagnosis of peptic ulcer of the stomach or duodenum is not difficult, but, as in most gastro-intestinal conditions, co-operation between the radiologist and the clinician pays a good dividend. Apart from the occasional difficulty in determining whether a gastric lesion is simple or malignant, the most common errors are failure to detect an ulcer on the posterior stomach wall, or a duodenal ulcer situated beyond the bulb. The first is liable to be missed if the stomach is rapidly filled with barium; but radiography in the lateral or prone instead of the orthodox supine position will almost invariably give a profile view of the lesion.

Difficulty in displaying the post-bulbar ulcer is occasioned by the backward inclination of the duodenal bulb; in the usual views the lesion is hidden by a normally filled duodenal cap, or even by the pyloric antrum. Oblique or lateral views, and especially stereoscopic radiography of the duodenum as suggested by Cummack (1952) resolve the difficulty, and may demonstrate a post-bulbar crater, or even a post-bulbar stenosis

The possibility of a lesion distal to the cap should always be considered when symptoms are atypical. The post-bulbar ulcer may present first as chronic or acute massive bleeding, or as an obstructive lesion associated with much vomiting, or as an ulcer-type dyspepsia with a large "back pain" component. Under such circumstances a negative radiological report following conventional radiology is worthless; indeed, in suspected gastroduodenal lesions, a negative radiological report is misleading unless the radiological specialist has observed the areas in every conceivable position.

Gastroscopy

Gastroscopic observation of the stomach has a limited place in the diagnosis of peptic ulcer, but the experienced endoscopist may be able to confirm the suspected malignancy of a gastric lesion or raise a suspicion that a clinically and radiologically simple ulcer is not innocent.

MEDICAL MANAGEMENT

Medical management seeks to relieve symptoms, to expedite the healing, and, if possible, to prevent recurrence of the ulcer; that is, to treat the ulcer disease. These aims, though not mutually incompatible, are not identical; those measures,

for instance, which relieve pain do not necessarily promote healing. Traditionally, management consists of rest, a bland diet, and antacids, to which are added drugs such as antispasmodics. The precise value of these measures has received little exact assessment. Doll, Friedlander and Pygott (1956) separated a group of patients with gastric ulcer into two groups and maintained one on a normal diet, while the other received the usual bland ulcer diet. The rate of healing of the ulcers was measured in the two groups and was the same, but there was greater symptomatic relief in the group treated on the bland diet. Doll and his colleagues (1956), in a further trial of ulcer healing, compared a standard ward diet with continuous milk drip administration. Again they were unable to demonstrate any difference in the rate of healing in the two groups, and there is so far no evidence to support the use of the traditional bland diet for this purpose.

SURGICAL MANAGEMENT

Just as the evidence suggests that in the pathogenesis the predominating factor is different in gastric and in duodenal ulcer, so there is general agreement that each poses a separate and distinct surgical problem.

Gastric Ulcer

In gastric ulcer the therapeutic object is the removal of a "sick" mucosa, rendered vulnerable to even a subnormal acid secretion. In practice this is successfully achieved by resection of the distal stomach and the lesser curve; and since the duodenum is either normal, or carries only the scar of a healed ulcer, restoration of continuity can usually be effected by anastomosis between the cut ends of stomach and duodenum—the Billroth I resection.

The results of the Billroth I resection for gastric ulcer are so satisfactory that it is sometimes urged that all stomach ulcers should be submitted to operation as the only certain way of distinguishing between an innocent and a malignant ulcer. However, since a proportion of the malignant ulcers seem to be detected only on careful histological study of the lesion, it would appear that operative inspection has its limitations also; and the fact is that in a considerable number of gastric ulcers the clinical, radiological, gastroscopic and cytological evidence so far justifies a presumption of innocence that non-operative treatment is permissible, and in some instances indicated. Fortunately, perhaps, the difficulty in deciding for or against surgery is more theoretical than real for the "simple" ulcers most likely to raise a suspicion of malignancy are precisely those that on other grounds—size, recurrence, haemorrhage, penetration and situation—require operation. In any event if any gastric ulcer treated medically is followed carefully until complete healing is unequivocally demonstrated, it is unlikely that more cancers will be missed than the number of patients who would die following gastric resection. It is, of course, axiomatic that unless healing is established beyond any doubt, operation is mandatory

Duodenal Ulcer

In duodenal ulcer, the only target so far uncovered is the gastric hypersecretion,

and the primary object of surgery is to reduce the acid secretion to a level at which the original ulcer is certain to heal and at which subsequent ulceration is unlikely. No matter how we seek to explain the excessive secretion, there are two surgical methods by which its reduction can be ensured—by resection of a sufficient part of the acid-producing mucosa, that is, partial gastrectomy, or by interruption of the stimuli that provoke gastric secretion, that is, vagotomy or excision of the gastric antrum, or both.

For all practical purposes other surgical procedures can be dismissed; though it is worth bearing in mind that gastrojejunostomy, the orthodox operation for duodenal ulcer in Great Britain until the last war, unquestionably promoted permanent healing of the ulcer, at a low cost in terms of mortality and morbidity, and, in rather more than half the cases, the long-term result was perfect. The operation was abandoned because of the high incidence of later ulceration at the stoma. It is possibly significant that the incidence of post-gastrojejunostomy stomal ulceration increases with the passage of time, so that it may still be too soon to put a final numerical value on the risk of stomal ulceration after gastrectomy.

Partial gastrectomy

Gastric resection is generally regarded as the operation of choice for duodenal ulcer. In general it is successful, and to some of its doughty protagonists any challenge to its routine employment is sacrilege. It has the merit of being logical, and of directly attacking the most likely cause of the high gastric secretion; that is, the parietal cell mass. Nevertheless, it is a mutilating operation, which is not invariably satisfactory, and it is well to be clear about its several defects.

The operative mortality following gastrectomy shows considerable variation. Recent publications report a death rate of 1 per cent (Clark and Kay, 1959); 2–3 per cent (Stammers, 1959), and 4·9 per cent (Crile, 1958). It is perhaps unwise when determining the "balance-sheet" of gastrectomy—or any operation, for that matter—to found on the experience in the best hands and assume that equally good results can be obtained by everyone. Crile's report is particularly valuable, therefore, and particularly appropriate as a profile of the position among average general surgeons and in clinics not especially concerned with gastric surgery. During the period of Crile's survey, 2,562 elective operations were undertaken for duodenal ulcer in general hospitals in Ohio. Mortality following gastrectomy ranged from nil to 7·8 per cent, with an average of 4·9 per cent. Alternative operations, including vagotomy and gastrojejunostomy, were attended by a mortality of 1·7 per cent. Attempting to assess the economics of gastric surgery, Crile found a recurrence rate of 5 per cent after vagotomy and gastrojejunostomy, and pointed out that if these patients were later submitted to gastrectomy, with the standard death rate the ultimate mortality would be 1·9 per cent as against a death rate of 4·9 following gastric resection—a difference as between 19 and 49 in 1,000 cases.

In those who survive gastrectomy, the end-result is unsatisfactory in about 22 per cent (Clark and Kay, 1959). This is remarkably good considering the obvious changes in gastric physiology that must follow the grossly altered

mechanical arrangements. These unsatisfactory results include. the various "post-gastrectomy syndromes"; late mechanical obstructions (Stammers, 1959); hypochromic anaemia, nutritional deficiencies with failure to gain weight, avitaminosis; the realighting of tuberculous pulmonary lesions; and recurrence of the peptic ulcer disease.

Dumping syndrome

This syndrome aroused little notice when it was first described by Hertz in 1913. It includes a variety of symptoms such as weakness, tachycardia, perspiration, flushing and nausea. These symptoms are uncommon after gastro-enterostomy alone, and their incidence is low when only a small portion of the stomach is resected. There is also general agreement that the symptoms occur in those patients in whom barium leaves the stomach rapidly, and the introduction of hyperosmolar solutions into the jejunum can be shown to reproduce the syndrome in a large number of instances. The use of 150 millilitres of 50 per cent glucose solution has been used for this purpose by a number of workers The introduction of such fluids into the jejunum was shown by Roberts and her colleagues (1954) to be accompanied by a fall in plasma volume of up to 1 litre. This fall in plasma volume was thought to be directly responsible for the vasomotor changes which form part of the syndrome. These findings were confirmed by Amdrup and Jorgensen (1957), who noted that the symptoms did not occur when their patients adopted a supine position, and that in this position the typical fall in plasma volume did not follow. They deduced that this was due to a slower emptying of the stomach, since when they introduced glucose solutions directly into the jejunum with the patient lying down, a typical attack appeared They also showed in rabbits that the amount of fluid appearing in the jejunum varied with the length of the jejunum into which the solution was injected. These experiments relate the symptoms to the extent to which the jejunum is filled with the hyperosmolar solution and therefore to the activity of the bowel. Jordan, Overton and DeBakey (1957) recorded tracings of the jejunum in patients with the dumping syndrome, and tried the effect of antispasmodic drugs They found that Banthine and hexamethonium were of therapeutic value, and that in 81 per cent of the tests in which inhibition of motility occurred, there was also relief of dumping symptoms. It should be emphasized that this train of symptoms can be produced in patients with intact stomachs if the hypertonic solution is introduced directly into the jejunum (Weidner and his colleagues, 1958) This hypothesis, that the syndrome is directly caused by change in plasma volume, has received increasing criticism. Peddie, Jordan and DeBakey (1958) were unable to show a good correlation between drop in plasma volume and the occurrence of symptoms, since two of their patients showed no change in plasma volume though manifesting all the classical symptoms The problem has been re-investigated by Webber, Bender and Moore (1957), who used the same stimulus, 150 millilitres of 50 per cent glucose administered orally, and confirmed that no patient without a history of the dumping syndrome showed symptoms under the conditions of the test However, the average drop in plasma volume in patients with symptoms was 150 millilitres, while the average drop in plasma volume in those patients without symptoms was greater, 194 millilitres, and there

was no correlation between these findings and the clinical history. Nor is it easy to imagine that changes in plasma volume to this extent are sufficient to produce the vasomotor symptoms.

Everson and Abrams (1958) found that one of their subjects, who had no clinical dumping symptoms and who did not have severe symptoms experimentally, had by far the greatest plasma volume decrease, 20·4 per cent. Further, if the symptoms are primarily related to a decrease in plasma volume, it would be surprising to find an increased peripheral flow, yet this is precisely what Hinshaw and his colleagues (1957) found. Morris, Greenfield and Jordan (1958), investigating the renal haemodynamics during dumping, found a post-prandial elevation in renal blood flow in 12 post-gastrectomy patients. It is difficult to fit in this finding with the concept of a contracted blood volume, and it would seem that the original theory was oversimplified. It seems more likely that the excitability of some vascular reflexes is the major factor, so that in the patients in whom the syndrome develops, the vascular reflexes develop more readily in response to the altered physiological conditions.

Bilious vomiting

This unpleasant and indeed distressing sequel to gastrectomy may be part of the "dumping syndrome" or be unaccompanied by other post-cibal symptoms. In many instances an organic partial obstruction sufficient to allow of the accumulation of bile and duodenal secretions cannot be identified, and elucidation of the cause must await further investigations. It is pertinent to recall, however, that direct anastomosis of the gall bladder to the stomach for malignant bile duct obstruction, or for the treatment of duodenal ulcer, was followed by bilious vomiting in only a proportion of cases, and it may be that some stomachs are more intolerant of bile than others, or that there is a factor of personal idiosyncrasy.

Attempts have been made to put some of the blame for these post-gastrectomy symptoms on the type of gastrectomy, or on its technical performance. In particular, there are some who favour a gastroduodenal anastomosis (Billroth I) to the more orthodox Polya operation. In most duodenal ulcers—or at least duodenal ulcers that require operation—a gastroduodenal anastomosis is technically impossible or surgically hazardous; and Goligher (1956) and others have shown that it causes a much higher recurrence rate (10–15 per cent). The same author found that the functional results were slightly better after the Polya operation; and that "dumping" was more common, and bilious vomiting slightly less after the Billroth I procedure. The experience of the authors is that the type or technique of the gastric resection or the subsequent anastomosis have no influence on the end-result, with the one proviso that very high gastrectomies are more commonly associated with poorer functional results.

Recurrent ulceration

As in the case of the post-operative mortality rates, the incidence of recurrent ulceration is variously stated to be from 1 per cent (Andersson, Elwin and Uvnäs, 1958) up to 5 per cent (Balint and his colleagues, 1957); and as time goes on, it may well be more.

The recurrent ulcer may be situated in the jejunum, at the stoma ("anastomotic"), or in the gastric remnant. In the authors' experience, the rare "anastomotic" ulcers have usually been associated with non-absorbable suture material in the bed of the ulcer. When the stoma is occluded by a balloon, and the maximal secretion from the gastric remnant is estimated, it is obvious that recurrent ulcer in the jejunum is associated with a secretion that despite the gastrectomy is still higher than that for the whole of the normal stomach, and sometimes higher than that for the intact stomach in primary duodenal ulceration. The jejunal ulcer, in fact, is *the result of gastric hypersecretion* This is not so when the ulcer is sited in the stomach; acid production is then subnormal, and the gastric lesion is again an expression of lowered resistance on the part of the stomach mucosa.

The fact that partial gastrectomy sometimes fails to reduce the gastric secretion to "safety" level is disturbing, particularly to those who have claimed that the operation was followed by all but complete achlorhydria, but is understandable in view of the amount of acid-producing tissue contained in the fundus and upper part of the body of the stomach. Indeed, in view of the distribution of parietal cells a few surgeons, influenced by the possibility of recurrent ulceration, have devised more drastic procedures than the standard gastrectomy for the resection of the acid-bearing part of the stomach—Visick's (1948) "measured radical" gastrectomy, Deloyers' (1956) "reversed" gastrectomy, and Wangensteen's (1957) tubular gastrectomy are examples.

These modifications as well as orthodox partial gastrectomy in the strictest sense of the term were "empirical", or at least uninformed, in so far as the "acid target" was not known quantitatively before operation, and the quantitative effect of operation was similarly unknown. In surgical jargon, gastrectomy reduced gastric acidity, but what acidity, and by how much was disturbingly vague Pre-operative study of gastric function and post-operative assessment of the acid response to maximal histamine stimulation now enable us both to define accurately the individual patient's exact requirement, and the extent to which operation has met it It seems that patients who develop jejunal ulcer after gastrectomy are those in whom a high pre-operative gastric secretory capacity is insufficiently reduced by a standard, normally adequate two-thirds or less gastrectomy The usual pattern of gastric resection may be expected to reduce the acid secretion by about 70 per cent, and since the majority of duodenal ulcer patients have only a moderately high secretory output, with a mean of 37·5 mEq of acid in the post-histamine hour, recurrent ulceration is unlikely to follow standard partial gastrectomy in such individuals.

On the other hand, there is a group of high secretors, possibly as many as 11 per cent (Bruce and his colleagues, 1959), amongst whom are the recurrent "ulcerators" and the persistent "perforators" described by Balint and Gummer (1958) In this group serious consideration has to be given to high gastrectomy, or near-total gastrectomy, or to a combination of standard gastrectomy with supplementary vagal denervation

It seems only right to insist that patients with duodenal ulcer should not be submitted to surgery without quantitative assessment of their gastric function, for only in the light of this knowledge can the surgeon decide on a method which

serves the patient's need. It is, in fact, now possible to "tailor" our gastric surgery to exact individual requirements.

Vagotomy

Division of the vagus nerves reduces the volume and the acidity of the gastric secretion to an extent comparable with standard gastrectomy, and is associated with immediate and complete relief from peptic ulcer symptoms. The operation also results in gastric stasis, and the consequent fermentation of food in the stomach gave rise to such unpleasant side effects that it was very soon apparent that to be useful in the treatment of duodenal ulcer, it had to be supplemented by some provision for drainage of the paralysed stomach—gastro-enterostomy or pyloroplasty.

Vagotomy with drainage has now been carried out sufficiently often and used for a sufficiently long period to justify comparison with partial gastrectomy (Burge and Pick, 1958). It seems beyond doubt that the proportion of completely satisfactory results is similar in the two methods; but the operative mortality after vagotomy is negligible, and apart from an occasional patient with transient dysphagia (Bruce and Small, 1959) the convalescence is easier. The operation is also less mutilating and less ruthless; and post-operative nutritional sequelae, anaemia and vitamin deficiencies, are rarely encountered. Mild "dumping" may be experienced, and bilious regurgitation also, though both are less frequent and much less severe than after gastrectomy. Burge and Pick found recurrent ulceration in 5 per cent, a figure that corresponds with that of Crile and with the authors' experience; this is within the range of published confession of recurrent ulcer after gastrectomy, though in individual experience the chances of recurrence are a little higher than after gastric resection. This may be related to the completeness of the vagal denervation. Burge and Vane (1958) evolved a method for testing the adequacy of the nerve section at operation, and their findings suggest that it may not be uncommon for small vagal strands to be left behind.

The principal ill-effect of vagotomy is post-operative diarrhoea, which occurs in 30 per cent of patients, and is sometimes very troublesome and disabling. Burge and Clark (1959) did not subscribe to the common view that this is caused by chronic bacterial infection secondary to gastric stasis and hypo-acidity; on the contrary, they believed it is due to denervation of the coeliac plexus, and that it can be avoided by leaving intact the coeliac division of the posterior vagus.

Most of the above observations refer to a combination of vagotomy and gastro-jejunostomy. Similar results (but no better) are obtained by vagotomy and pylorectomy (Herrington, 1958); but since this procedure adds some of the hazards of gastric resection, without seeming to carry any added advantage, it is unlikely to replace the simpler combination. However, it does raise the interesting point, what exactly is the antrum? There are no guides to the extent of this part of the stomach, and antral type of mucosa certainly extends on the lesser curve for a variable distance proximal to the incisura angularis, the boundary of the orthodox anatomy. Landboe-Christensen (1944) from a study of a series of stomachs concluded that histologically the antrum included 44 per cent of the lesser and 12 per cent of the greater curvature, which seems to define the limit of distal resection for antrectomy

at a line from the midpoint of the lesser curve to the junction of the distal third and proximal two-thirds of the greater curvature.

Selection of operation for duodenal ulceration

The evidence suggests that in the large majority of duodenal ulcer patients, who are only moderate hypersecretors, either partial gastrectomy or vagotomy with gastrojejunostomy give remarkably comparable results and in the future most surgeons will opt for the method that in their own hands carries the lower death rate, the smaller recurrence rate and the least post-operative morbidity At the moment, vagotomy with gastro-enterostomy is gaining in popularity, not the least of its advantages being the possibility of later gastrectomy should it fail. But even those who are stubborn and staunch gastrectomists must concede that even if vagotomy with gastrojejunostomy is not to be countenanced as routine treatment, the operation has a definite place in those patients who do less well with partial gastrectomy: women, with their particular liability to severe anaemia, the very young, in whom it is important to avoid undernutrition, the elderly patients with stenosis in whom the risks of gastrectomy are greater, and those with healed pulmonary tuberculosis that may be rekindled by post-gastrectomy nutritional disturbances. Furthermore, when at operation the ulcer and the tissues around it are found to be oedematous and inflamed, so that resection is hazardous, vagotomy and gastrojejunostomy is a safe and satisfactory alternative to two-stage resection or a gastrectomy modified after the fashion of Bancroft.

In the small group of duodenal ulcer subjects whose secretion is very high neither gastrectomy alone nor vagotomy with drainage alone are adequate to guarantee against recurrent ulceration, though a combination of high gastrectomy and vagotomy may hold out greater prospect of success. It is in this group that in the future we may have to look further afield than the stomach, that we may have to consider an endocrine factor, especially when jejunal ulcer reappears despite very adequate and even radical surgery

In conclusion, it is a fair judgment that all surgery for duodenal ulcer is to a greater or less extent mutilating, and must one day be superseded by curative medical methods In the meantime, the evolution of tests for the quantitative assessment of gastric secretory function, and the consequent opportunity of treating each duodenal ulcer patient as an individual problem represents the most important single advance in our approach to this problem since Dragstedt in the face of distinguished and authoritative opposition revived and established the operation of vagotomy

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SURVEY ON PARTIAL HEPATECTOMY WITH ESPECIAL REFERENCE TO LIVER ANATOMY

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ANATOMICAL CONSIDERATIONS

Internal hepatic architecture is based upon the scaffolding of the four sets of vessels that traverse the liver substance. These vessels, the hepatic veins, portal veins, hepatic arteries and bile ducts, are each arranged in segmental fashion. However, subdivision of the liver into surgically important fractions is complicated *by the fact that the hepatic veins are disposed in one pattern, while the other three* sets of vessels follow another which is quite different.

Hepatic venous system

The hepatic veins, by their size, dominate the scaffolding. The capacity of the hepatic venous system is more than twice that of the portal venous system, which is itself much larger than the bile ducts and arteries There are three major hepatic veins, a right, a central and a left (Fig. 3). As they traverse the liver they pass upwards and slightly backwards to converge on the inferior vena cava at the superior margin of the [illegible] vein *enters the left hepatic* [illegible] cava itself. Lesser hepatic [illegible] ls to enter the inferior vena cava at various levels below the main hepatic veins are not very important anatomically. However, their proximity to the vena cava and the difficulty of isolating more than a very short segment of their course between liver and vena cava for the application of ligatures magnifies their surgical significance.

Glissonian system

Once the immediate neighbourhood of the porta hepatis has been left the branches of the portal veins, hepatic arteries and bile ducts run through the parenchyma in a close mutual association. Within the liver substance each branch of the portal vein with its associated smaller bile duct and hepatic artery is invested

so that in many places these branches are in fact at right angles to the neighbouring hepatic vein branches. Moreover, the primary division of the Glissonian system, unlike the hepatic venous system with its three major vessels, is into two branches, a right and a left.

Subdivision of the liver

There are no gross anastomoses between neighbouring vessels of any group, whether hepatic veins, portal veins, bile ducts or hepatic arteries. It is therefore possible to subdivide the liver in two separate ways, depending upon whether the hepatic vein system or the Glissonian system is chosen as the basis for subdivision.

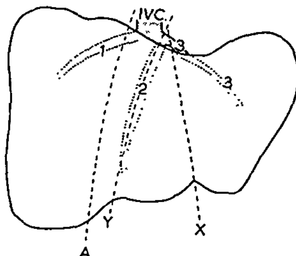


FIG. 4 —Position of the principal plane (Y) and the plane of the falciform ligament (X) on the anterior surface of the liver The line of section in right hemihepatectomy is shown (A). Note that the central hepatic vein (2) lies in the principal plane and that only if the left hepatic vein (3) is secured to the left of the falciform ligament is there no danger of damaging the central vein during left lobectomy (*see* key, Fig. 3).

The three hepatic veins may be said to define three *territories*, a left, a middle and a right; notice in Fig. 3 that the left territory corresponds to that part of the liver to the left of the plane of attachment of the falciform ligament. In contrast, subdivision based on the Glissonian system divides *the liver first into a right and* a left *segment.*

The principal plane

These two primary Glissonian segments are approximately equal in size, and it is for these entities that the terms right and left halves of the liver should be reserved. The plane separating one from the other may be called the principal plane. The position of this plane was first described by Rex (1888), and Cantlie (1898). Descriptions of the principal plane have usually depended upon studies

with casts of the hollow structures, but it has recently been found possible to visualize the plane by injection of the main right and left bile ducts with differently coloured aqueous dyes. Each dye diffuses through to the surface only in the segment drained by the duct into which the dye was injected (For a colour plate of such a specimen, *see* Hobsley, 1958.) Fig. 4 shows that on the anterior surface the principal plane extends from the apex of the gall-bladder notch at the lower border, vertically upwards as an approximately straight line. At the upper border of the liver, its surface marking is the point of entry of the left hepatic vein into the inferior vena cava. On the posterior aspect, the line bisects the caudate lobe and the gall-bladder bed Fairly definite landmarks do, therefore, enable the principal plane to be defined on both surfaces of any liver, but its position is not very constant in the upper half of the anterior surface

The central hepatic vein lies in the principal plane: this relationship is surgically unfortunate, since it means that the territory of the central hepatic vein is partly in the right half of the liver, partly in the left

Plane of the falciform ligament

There is, however, one plane of subdivision of the liver which is common to both hepatic vein and Glissonian systems; the plane of the falciform ligament. As previously noted, and illustrated by Figs. 3 and 4, the plane of the falciform ligament separates the territories of the left and central hepatic veins It also separates the left half into left and right subsegments Fig 5 diagrammatically represents the commonest pattern of branching of the biliary tree; no important bile duct branches cross the plane of the falciform ligament except the main continuation of the bile duct to the left lobe. The same is true of the arterial and the portal venous systems (Fig. 3) Thus the part of the liver to the left of the plane of the falciform ligament has its own separate vasculature with reference both to the hepatic venous and to the Glissonian systems The usual terminology by which the liver is subdivided into *right* and *left lobes* separated by the plane of the falciform ligament is thus justified in this special sense.

Further subdivision

Attempts have been made, for example, Couinaud (1957) and Gans (1955), to carry to greater lengths the subdivision of the liver according to the Glissonian system. For example, Fig. 5 indicates that the *right half* of the liver has two separate Glissonian pedicles, and corresponding with these two pedicles it has been suggested that the right half should be subdivided into antero-medial and postero-lateral segments. However, aqueous dye injection studies described elsewhere (Hobsley, 1958) suggest that the surgical importance of such a subdivision is limited· the surface of separation between the segments describes a complicated curve; there is no anatomical landmark that might act as a sure guide to the position of the boundary; and there is much intermingling, though no anastomosis, near the right extremity of the liver. Fig 5, however, may serve to remind the surgeon performing a limited operation on liver substance of the directions in which the Glissonian structures locally run.

Surgical applications

Formal left lobectomy

From the foregoing description it follows that the only f[illegible] possible (defined as removal of [illegible] pedicle and the Gl[illegible] Formal [illegible] hepatic vein and (2) the Glisson[illegible]

In tying the left hepatic vein at the superior border of the liver, damage to the central vein, which may enter the left vein, must be avoided. The ligature is, therefore, performed at, or to the left of, the falciform ligament. As regards the

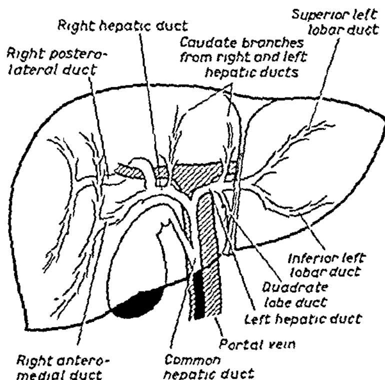


FIG. 5.—The commonest [illegible] viewed [illegible] (by courtesy of the [illegible] of The British Journal of Surgery.)

Glissonian pedicle, Fig. 6 shows that the left lobe is supplied by [illegible] vein branches which arise at the left [illegible] blunt [illegible] sp[illegible] he[illegible] because they are more superficial th[illegible] Glissonian structures and their destination is usually frankly

signalled by their direction at an early stage of their course. The Glissonian pedicle to the left of the saccus may be controlled by the mattress suture method described below. When both pedicles have been secured the liver may be transected along the plane of the falciform ligament with minimum danger of haemorrhage, or of leaving *in situ* hepatic tissue which has been deprived of blood supply or biliary drainage. This Glissonian pedicle should not be tied any nearer the bifurcation of the portal vein, that is, to the right of the plane of the falciform ligament; such a procedure would threaten the viability of the quadrate lobe and half the caudate lobe (Figs 5 and 6).

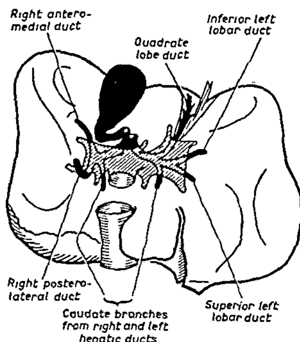


FIG. 6 —The liver has been turned upwards to show a common arrangement of structures in the portal fissure Note the left division of the portal vein turning forwards to terminate as the blunt saccus, and the curve of the postero-lateral duct over the right division. (*By courtesy of the Editor of The British Journal of Surgery*)

Hemihepatectomy

Hemihepatectomy is removal of half the liver with section performed approximately along the principal plane. Theoretically, both right and left hemihepatectomy are possible; in each case the main Glissonian pedicle, and the corresponding right or left hepatic vein, can be completely controlled. The central vein, however, must be preserved so as to safeguard that half of the central vein territory which is being left *in situ*. It follows that the actual line of section must be a little to one or other side of the principal plane (in which the central vein lies), to the right in right hemihepatectomy, to the left in left hemihepatectomy.

In the latter operation the line of section will be almost at the falciform ligament (*see* Fig. 4), and it is difficult to imagine circumstances in which the extra risk of left hemihepatectomy, as compared with the technically simpler left lobectomy, will be outweighed by the slightly wider excision achieved. (The greater risk of hemihepatectomy is due to two factors: first, the greater thickness of the liver in this region; secondly, the proximity of the large central hepatic vein.)

During a hemihepatectomy, the Glissonian pedicle should be secured as far to the ipsilateral side of the bifurcation of the common portal vein as possible. Healey and Schroy (1953) remarked that in no less than 28 of 100 livers the bile

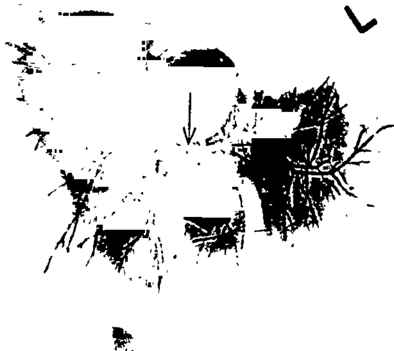


Fig. 7.—Post-mortem cholangiogram The right postero-lateral duct (arrowed) takes separate origin from what is apparently the *left* hepatic duct. (*By courtesy of the Editor of The British Journal of Surgery.*)

duct draining either the antero-medial or the postero-lateral segment of the right half arises from the left hepatic duct. Fig 7 is a post-mortem cholangiogram showing an example of this pattern. in such a case it would be very easy, in performing a left hemihepatectomy, to apply a ligature to the left hepatic duct proximal to the origin of the right postero-lateral duct, thereby depriving of its biliary drainage half the bulk of liver remaining after the operation.

Summary of the anatomical considerations

The plane of the falciform ligament is the best surgical plane in the liver, and left lobectomy is performed at this plane The left hepatic vein is tied at, or to the left of, the plane; thereby damage to the central hepatic vein is avoided.

In right hemihepatectomy, the right hepatic vein is tied, but the central vein carefully preserved, a plane of section is chosen somewhat to the right of the principal plane. The Glissonian pedicle should be tied as far to the right as possible.

Left hemihepatectomy is practicable, but may be dangerous, it is not further considered here.

PARTIAL HEPATECTOMY

Indications

The main indication for partial hepatectomy is primary malignant disease (hepatomas and cholangiomas) which is rare in Europeans but more commonly found in Africa and China where nutritional cirrhosis appears to be the predisposing factor. The chances of finding a primary liver cancer at an early stage and suitably isolated in one lobe is still remote since there are as yet no tests to provide an early diagnosis There have, however, been a number of recorded successful operations with apparent cures

Hepatectomy may also be indicated for a solitary metastasis such as that from a primary growth in the large bowel provided that the tumour is not of high grade malignancy. In cases where a solitary metastasis is found some considerable time after the removal of the primary growth, hepatic lobectomy may be justifiable since there is a greater chance of the metastasis being in fact the only one There is by then, however, the added risk of dissemination to the lungs and the lung fields should be carefully checked before embarking upon the operation.

In patients with direct extension of primary tumours of the stomach, gall bladder or hepatic flexure of colon into the liver some form of hepatectomy may occasionally be considered and of these it is the patients with colon tumours who are the most likely to derive worthwhile benefit

Carcinoma of the gall bladder is frequently undetected until invasion of the porta hepatis has resulted in jaundice. Although there has been some enthusiasm for dealing with these cases by a right lobectomy operation, there have been no promising results Patients without jaundice in whom the carcinoma is discovered by chance at an exploratory laparotomy should give more rewarding results

Contra-indications

Patients with benign tumours such as simple cysts and angiomas do not require surgical treatment. Multiple metastatic tumours in one lobe are so frequently associated with undetectable deposits in the opposite lobe that any reasonable hope of total ablation of the disease is too remote to warrant a lobectomy. The gross cirrhosis of the opposite lobe that is often associated with hepatomas contra-indicates any operation.

No operation should be contemplated when liver function tests persistently indicate liver parenchymal damage or failure.

Categories of operation

Local removal of tumours with direct extension into the liver

In this type of operation the principle of mass mattress sutures beyond the line of transection is used. These sutures should be strong chromic catgut (No. 2 or 3) firmly but never tightly tied and the mattress may be overlocking or interlocking as in a Goodsall's ligature. Large curved liver needles or blunt ended large five-eighths circle needles will be found to be the most useful.

Local removal of the small metastasis

There must always be some doubt regarding the singularity of small metastases. When they are easily approached there may be some justification for their removal and in the fit patient the splitting of the costal margin can be readily undertaken and provides considerable improvement of access.

On the rare occasion when a metastasis of this order is found some time after the removal of the primary growth one may be more certain of the limits of the metastatic spread and then removal may warrant an operation on a bigger scale, for example, the use of a thoraco-abdominal incision for those tumours on the dome of the liver.

The operation site should be surrounded by firmly placed packs and constant suction used to obtain a clear field and to estimate blood loss. Haemorrhage is controlled by surrounding mattress sutures placed in position before liver division and the gap closed by further mattress sutures.

Left lobectomy

Left lobectomy is indicated when a single, often large, deposit is found in the left lobe, the remaining liver and the lungs being apparently normal The operation advised is the removal not of the left half of the liver but of the left lobe, that is, that part of the liver which lies on the left of the falciform ligament.

The operation is carried out through a right upper paramedian incision and it may be necessary to improve this access either by splitting the lower part of the sternum or by dividing the right costal margin.

The round ligament is divided and the left lobe exposed. Duval's forceps will be found useful for holding the liver substance. The lobe is mobilized by dividing the left triangular ligament and the falciform ligament, care being taken not to injure the left hepatic vein which lies just posterior to the junction of these two ligaments On one occasion one of us (O. V. L.-D.) had the misfortune to damage this vein and had to ligate it hurriedly near its entry into the vena cava without realizing the consequences. The patient had a very stormy convalescence and eventually discharged a large slough of what must have been liver tissue due no doubt to inclusion of the central vein in the ligature.

If the left hepatic vein is ligated separately this should be done to the left of the falciform ligament and there is then no risk of including the central vein.

A Payr's non-crushing intestinal clamp mounted with small knobs and originally designed by Child, a Portsmouth surgeon, will be found to hold liver tissue with a firm grip and the minimum of trauma (Fig. 8); and this is now applied across the liver substance at the level of the divided falciform ligament. With the clamp

in position the liver can be drawn forwards into the wound whilst catgut mattress sutures of the Goodsall type are placed behind the clamp. The liver is then divided just distal to the clamp (Fig. 9) which is then removed. As a rule only a few individual vessels require ligation.

The cut liver surface is covered by suturing the remaining fringe of the falciform ligament to gastro-hepatic omentum and the area drained with corrugated rubber

Right hemihepatectomy

For the operation of right hemihepatectomy to be successful and for blood loss to be minimal it is important to devise an orderly technique and to divide all the main vessels to and from the lobe before dividing liver substance The main points may be summarized as follows.



FIG 8.—Payr's clamp modified by Child



FIG. 9.—Left lobectomy with clamp and ligatures *in situ*.

The patient should be placed in the half-left lateral position so that by tilting the table a full-left lateral or supine position can be obtained during the various stages of the operation.

A thoraco-abdominal incision is essential to give adequate exposure The diaphragm is divided from the incised costal margin to the vena cava foramen. This allows the liver to fall into the chest and enhances the view of the portal fissure

The first step should be a careful dissection of the porta hepatis whilst the field is dry. The cystic duct and artery are divided between ligatures, followed by division of the right hepatic duct and artery in a similar manner. Owing to the

short trunk of the right portal vein it may be advisable to leave its division to a later stage.

At this stage controlling tapes are passed around the vena cava above the renal veins and just above the diaphragm to minimize blood loss should the vena cava be damaged.

The patient is now tilted into the left lateral position to allow the liver to fall to that side. The right triangular ligament and anterior and posterior layers of the



Fig. 10.—Shows a tongue-like process of liver which obscures the right hepatic vein. Controlling tapes around the inferior vena cava and short hepatic veins have been divided. (*By courtesy of the Editor of The British Journal of Surgery.*)

coronary ligament are divided thus completely freeing the right lobe from the diaphragm.

The right lobe is now displaced to the left, exposing the vena cava in its fossa and also displaying the short hepatic veins which are divided between ligatures *from below upwards.* About 2 centimetres below the diaphragm a tongue-like process of liver tissue, occasionally fibrotic, will be seen wrapping round the vena

cava and obscuring the right hepatic vein (Fig. 10). It is quite often adherent and requires careful freeing to avoid damage to either vena cava or right hepatic vein.

The inferior border of the right hepatic vein is now visible (Fig. 11) and by careful blunt dissection a curved artery forceps is passed along its medial aspect to emerge above the liver to the right of the left hepatic vein. The right hepatic vein is tied flush with the inferior vena cava and its very short extra-hepatic course often precludes a safe distal ligature so that the distal end is best dealt with by clamping the vein within the liver substance.



FIG 11.—Shows the exposed right hepatic vein before division (*By courtesy of the Editor of The British Journal of Surgery.*)

The patient is now turned into the supine position, the porta hepatis again exposed and the right branch of the portal vein isolated. Owing to its very short extra-hepatic course it is divided between a ligature and a clamp in a similar manner to the right hepatic vein

The liver is now divided with a scalpel along a line from vena cava foramen to gall bladder fossa as described in the anatomical text above, that is, just to the right of the principal plane. Individual vessels, mainly central vein branches, are picked up en route and tied later. Finally, the cut surface is compressed with mattress sutures. Partial covering of the raw surface can be obtained by reflecting the round ligament and the lower part of the falciform ligament.

There will inevitably be some biliary leakage from the cut surface and particularly so if the surgeon is obliged, on account of the position of the tumour, to include a portion of the left half of the liver. To minimize this a T-tube is placed in the common bile duct A large corrugated drain is placed under the repaired diaphragm and the wounds closed with a negative pressure drain in the pleural cavity.

Results

Liver resection for hepatomas in the absence of cirrhosis appears to give quite promising results. With metastatic tumours the results are not as promising, primarily because of undetectable spread into the lungs but in carefully selected cases, that is, in patients with a single metastasis and no apparent spread elsewhere, these operations may be well worth while.

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CHRONIC PANCREATITIS PATHOLOGICAL AND CLINICAL ASPECTS

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INTRODUCTION

The widespread belief amongst clinicians that pancreatic disease is difficult to diagnose has frequently resulted in a neglect of surgical treatment Similarly, a failure to relate treatment of such disease to the basic pathological processes occurring in the pancreas has led to the multiplication of ingenious but empirical operations As a result, our present understanding of chronic disease of the pancreas is inadequate The discussion which follows therefore deals mainly with pathological aspects of chronic pancreatic disease, with a short account of their clinical features and of some of the operative procedures at present available in this expanding field

PATHOLOGICAL CLASSIFICATION OF CHRONIC PANCREATIC DISEASE ("CHRONIC PANCREATITIS")

(1) Chronic relapsing pancreatitis.
(2) Primary pancreatic lithiasis
(3) Pancreatic lesions due to ductal obstruction ("pancreatosis")
(4) Non-specific pancreatic fibrosis.

Chronic relapsing pancreatitis

This term is applied to a clinical syndrome in which recurrent exacerbations of pancreatitis occur as a sequel to a prior attack of acute pancreatic necrosis The progressive damage to the pancreas results eventually in marked impairment of both exocrine and endocrine functions of the organ, but pain is frequently a predominant symptom Pancreatic calcification or stone formation occurs in about 40 per cent of cases.

Primary pancreatic lithiasis

The development of stones within the pancreatic ducts in this condition occurs without initial evidence of any parenchymal disease in the pancreas and is often symptomless The obstruction produced by the calculi may lead to progressive destruction of the parenchyma, with resulting widespread effects.

Pancreatic lesions due to ductal obstruction ("pancreatosis")

"Pancreatosis" denotes the pathological lesions which occur in the pancreas when the ducts are obstructed from any cause. Acinar replacement fibrosis and ductal dilatation predominate in this condition, a non-specific picture which may complicate ductal obstruction from a variety of lesions. The state is frequently encountered by the surgeon.

Non-specific pancreatic fibrosis

Pancreatic lesions are encountered in a variety of general medical conditions which include haemochromatosis, kwashiorkor and primary liver disease. Congenital cystic pancreatic fibrosis, although occasionally within the realm of the general surgeon called upon to treat infants, lies outside the scope of the present review.

The term "chronic pancreatitis" has unfortunately been used frequently to describe all of the four conditions briefly outlined in the above classification. The resulting confusion has delayed understanding of pancreatic disease. For this reason, in the discussion which follows, the term will be replaced by the more cumbersome, but less inaccurate descriptions given above.

CHRONIC RELAPSING PANCREATITIS

Aetiological factors

This syndrome follows approximately 10 per cent of attacks of sublethal acute pancreatic necrosis Once the disease has become established, it is generally impossible to determine the cause of the initial attack. However, it is now clear that the usual cause of acute necrosis in the pancreas is activation of pancreatic ferments which have extravasated into the interstitial tissue and this may follow sudden obstruction to the main ducts during active secretion, acute local vascular lesions and pathological changes in the lining of the pancreatic ducts (MacKenzie and Willox, 1956) The classical finding of Rich and Duff (1936) of an increased incidence of metaplastic epithelial lesions in the pancreatic ducts of patients dying from acute necrosis is of considerable significance. Their most important conclusion relates to the route afforded by the epithelial plaques for escape of secretion from the ducts A recent investigation in routine necropsy material has not only confirmed that such metaplastic lesions are common histological variants in the pancreas, but that they are often associated with gross dilatation of the minor pancreatic ducts (Birnstingl, 1959a). These structural changes sometimes produce an appearance of "pancreatectasis", readily demonstrated by pancreatography (see Fig. 12) and occur in organs which, in addition to the metaplastic changes, are the seat of widespread glandular epithelial hyperplasia resembling that encountered in the gall-bladder and usually described as "cholecystitis glandularis proliferans". It is at once apparent that rupture of these dilated, thin-walled spaces affords a ready means, upon a sudden rise of intraductal pressure from secretory stimulation or sudden obstruction, for the escape of pancreatic ferments into the interstitial tissue. Hyperplastic epithelial changes in the ducts have been described in patients dying with acute pancreatic necrosis and also in chronic relapsing pancreatitis, in which condition they may play some part in the recurrence of the disease

(Yotuyanagi, 1936, Edmondson, Bullock and Mehl, 1950, Wainwright, 1951). The association of hyperplastic and other epithelial changes with pancreatic necrosis requires further study.

It is difficult to explain the tendency of a few patients with pancreatic necrosis to develop further attacks. Gross, Comfort and Ulrich (1958) have published findings in two families in which an hereditary factor leading to the development of relapsing pancreatitis was apparently present. The disease in these examples

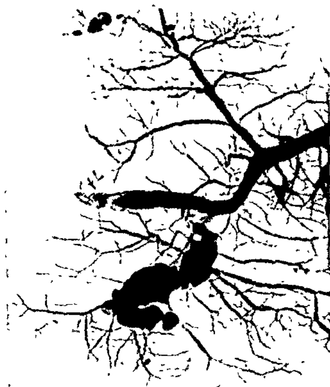


Fig 12.—Pancreatectasis of isolated secondary duct in lower part of head of pancreas Post-mortem pancreatogram The patient, aged 67 years, had no symptoms of pancreatic disease during life (The top arrow indicates the accessory pancreatic duct, the bottom arrow indicates the main pancreatic duct.) (By courtesy of the Editor of British Journal of Surgery.)

became manifest earlier in life than in the usual sporadic case, sometimes starting during childhood. However, in the vast majority of cases, no familial element is present and although a number of different factors probably contribute to the exacerbations, biliary reflux into the pancreatic ducts appears to be the most important. Although acute pancreatic necrosis occurs quite often in organs in which a "common channel" for bile and pancreatic secretions is absent, pancreatographic studies in patients with relapsing pancreatitis reveal that such a pathway

is present very frequently (Doubilet, 1956; Smith, 1957). Moreover, the results of biliary diversion procedures in preventing exacerbations in early cases of relapsing pancreatitis further suggest that biliary regurgitation may have been operative in these patients. A recent experimental study by Elliott, Williams and Zollinger (1957) has demonstrated the deleterious effect of bile in the pancreas under certain conditions It is well known that interchange of bile and pancreatic secretions occurs frequently and that injection of normal bile into the pancreatic ducts at physiological pressures is harmless. However, Zollinger found that bile could be activated by incubation for several hours with pancreatic juice. When the mixture was subsequently introduced into the ducts of dogs at normal pressures, fatal haemorrhagic pancreatic necrosis ensued.

The incidence of chronic relapsing pancreatitis appears to be considerably greater in the United States than it is in Great Britain and this may be related to the prevalence of chronic alcoholism there. The alcoholic subject is particularly liable to the development of acute pancreatic necrosis, which is followed by relapsing pancreatitis in about 10 per cent of cases. The reason for the association with alcohol is not known and there seems to be no evidence for any nutritional basis, comparable to alcoholic cirrhosis of the liver. Interstitial fibrosis of the pancreas occurs in certain states of prolonged protein deficiency, such as kwashiorkor (Davies, 1948) and lesions can be produced in animals by administration of an amino acid, dl-ethionine, which causes interference with the metabolism of the acinar cells. Although remarkably rapid atrophy of the acini can be produced in this way and may be complicated in the dog by the onset of haemorrhagic necrosis (Almeida and Grossman, 1952), this should probably be regarded as one of the artificial methods of initiating acute lesions in the pancreas, rather than resembling any known clinical state.

Morbid anatomy

The changes in the pancreas in the early case of relapsing pancreatitis are similar to those seen in acute pancreatic necrosis of sublethal intensity. The organ is enlarged and firm, whilst areas of previous haemorrhage and fat necrosis are characteristic. The latter are not confined to the pancreas itself and are often seen in the surrounding adipose tissue, particularly in the lesser sac of peritoneum The disease is frequently segmental, involving only parts of the organ.

As the condition becomes more advanced, secondary effects become superimposed upon the parenchymal destruction produced by the exacerbations of pancreatic necrosis. Pseudocyst formation, particularly in the head of the gland, is common and as a result of ductal stasis and possibly infection, stones may develop. This secondary pancreatic lithiasis is seen in about 40 per cent of patients with relapsing pancreatitis; the stones have a high calcium content and when present are readily seen on plain radiography of the abdomen. It is now apparent that pancreatic calcification of this type is invariably situated within epithelial [illegible] was formerly believed, in areas of fat [illegible] 950).

[illegible] many cases of relapsing pancreatitis should be considered a result of the disease and not its cause. Thus, although ductal

dilatation is a very common pathological finding, it is often unaccompanied by any demonstrable mechanical obstruction. In other specimens, however, obvious obstruction by calculi or inspissated debris, or by ductal distortion, is present and the combined effect of such blockage contributes markedly to both the symptoms and to the progress of the disorder. In this respect, ductal obstruction is liable to produce a peculiarly intractable, deep-seated type of pain and also to cause widespread atrophy of the parenchyma of the gland with resulting secretory insufficiency.

A study of the morbid anatomy of the pancreas from patients with chronic relapsing pancreatitis reveals the operation of several distinct pathological processes in the established case of the disease. The progressive nature of the untreated condition is to a large extent due to the interaction of these various factors, some of which are shown in the diagram (Fig. 13), although this doubtless represents an oversimplification It follows, nevertheless, that whereas in the early case of the disease surgical measures are directed towards reducing the frequency of the recurrent exacerbations of pancreatic damage due to necrosis, treatment in the

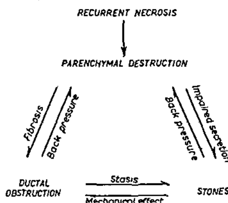


FIG. 13—Pathological factors in established chronic relapsing pancreatitis.

established case should aim to break this vicious circle, in which the exclusion of ductal obstruction, or its relief where present, is of paramount importance

Clinical features

The usual presenting feature of this syndrome is recurrent exacerbations of parenchymal inflammation, identical in every way with isolated episodes of acute pancreatic necrosis The condition therefore seldom develops without previous distinct attacks of abdominal pain. The pain is of the characteristic type associated with pancreatic disease and occurs in the upper central abdomen, usually with radiation to the centre of the back and one or both loins The patient often obtains some relief by adopting the erect sitting position. During the acute attacks, nausea and vomiting are present and are associated with a variable degree of intestinal ileus Obstructive jaundice, due to compression of the common duct by oedema in the head of the pancreas, occurs at some period in about 25 per cent of cases of relapsing pancreatitis and is generally of mild degree.

The damage produced in the pancreas by successive attacks leads to certain sequelae, which eventually predominate in the clinical picture over the earlier symptoms accompanying the relapses. In place of repeated episodes of acute necrosis, the patient with the more advanced disease comes to suffer from what, for lack of any more precise term, might be called a condition of "painful pancreatic insufficiency". The intermittent pain of the earlier stages of relapsing pancreatitis appears to be mainly due to oedema of the parenchyma during the exacerbations, but in more advanced cases, a continuous type of pain often occurs, which is due to obstruction of the pancreatic ducts. That this is the case may be shown by the relief afforded by decompression of the ducts and the reproduction of the pain in some cases by applying pressure to the duct system through a polythene cannula inserted for the purpose of pancreatography. Ductal obstruction in these patients is often accompanied by stone formation, the aetiology of which is probably complex. However, their development has the effect of further increasing the degree of any ductal obstruction already present (Fig. 13).

The pancreatic insufficiency which accompanies the advanced stages of relapsing pancreatitis is due to destruction of both the acini and the islets of Langerhans, but regenerative activity is well-marked and as a rule only patients with severe disease develop marked weight-loss, diarrhoea or glycosuria. In Comfort's classical description of 29 patients, glycosuria was detected at some stage in seven (34 per cent) (Comfort, Gambill and Baggenstoss, 1946). Steatorrhoea and creatorrhoea occur only in advanced cases

Diagnosis

Failure to diagnose chronic relapsing pancreatitis has in the past been largely due to lack of awareness of the syndrome on the part of clinicians, and although the disease may give rise to a number of clinical manifestations, its symptoms, of which abdominal pain is usually the principal, fall into a pattern which is very characteristic. Nevertheless, physical signs are generally not obvious on abdominal examination and confirmation of the diagnosis depends upon a number of special investigations.

Radiology

The existence of pancreatic calcification in approximately 40 per cent of patients with relapsing pancreatitis, makes confirmation easy in those cases in which it occurs. However, even when plain abdominal radiography yields negative results, great assistance may often be obtained by barium meal examination, particularly when carried out by a radiologist with experience in this field. In a small series of patients studied, radiological changes in the configuration of the duodenal loop were reported in 5 of 6 patients with relapsing pancreatitis subjected to this examination (Birnstingl, 1959b). The common appearances included displacement of the duodenum and stomach, deformity due to cyst formation and the demonstration of "irritability" of the duodenum as a result of oedema of surrounding structures during an exacerbation of pancreatitis. Although the importance of barium examination is now well established in the diagnosis of malignant disease of the pancreas, its application in other conditions affecting the organ is still insufficiently recognized.

Glucose tolerance test

This investigation is particularly important in distinguishing the steatorrhoea of advanced pancreatic disease from that due to other causes; in relapsing pancreatitis a diabetic or prediabetic tolerance is often obtained, whereas in other malabsorption syndromes, such as non-tropical sprue, a flat curve is generally present

Duodenal intubation

The value of duodenal sampling and the result of stimulation of pancreatic secretion by secretin and pancreozymin have been well studied by Marks and Tompsett (1958) The test is an elaborate one and is not usually required, since pancreatic secretory impairment is only revealed when acinar destruction is advanced, at which time the diagnosis is usually obvious on other grounds

Serum amylase

Elevations in the level of the serum amylase are seen only during the acute exacerbations in the early course of the disease; this investigation is seldom useful in the established case.

PRIMARY PANCREATIC LITHIASIS

Although most cases of pancreatic calcification occur as the result of repeated attacks of pancreatic necrosis, patients are occasionally seen in whom these changes are an accidental radiological finding and who give no previous history of abdominal symptoms. In these patients, multiple stones of high calcium content, and composed of a mixture of phosphates and carbonates, develop within the main and secondary ducts of the pancreas. The parenchyma is initially normal, but as a result of the combined effects of ductal obstruction and infection, considerable fibrous replacement may occur and some of the patients develop diabetes mellitus Although the stones are sometimes symptomless, they can give rise to pain, which may be severe.

The cause of the stone formation is obscure in most instances, but a number of cases have been published in which it has been associated with hyperparathyroidism (*see* Fig. 14). Primary pancreatic lithiasis is a rare condition, but when encountered it is worth estimating the serum calcium level, to endeavour to exclude this unusual manifestation of parathyroid adenoma (Cope and his colleagues, 1957, Hoar and Gorlin, 1958)

PANCREATIC LESIONS DUE TO DUCTAL OBSTRUCTION ("PANCREATOSIS")

The effect of obstruction to any part of the pancreatic ductal system is to produce interstitial oedema, followed by rapid and progressive atrophy of the acinar tissue in the related area of parenchyma, accompanied by fibrous replacement of the disappearing acini

Changes in the ducts

The changes in the ducts themselves depend upon the size of channel which is obstructed, but a very marked degree of dilatation may occur when the major ducts are involved and such enlargement is greatest when the block lies in the

region of the head of the pancreas. This dilatation may be absent when an alternative pathway for the escape of secretions is present, as provided by a patent accessory pancreatic duct or a pseudocyst communicating with the ducts (Fig. 15).

Changes in the pancreas

The changes in the pancreas following ductal obstruction may be readily produced in animals and the recognition of these lesions is of considerable importance in the diagnosis *of the precise pathological condition underlying pancreatic disease.* In the initial period following obstruction, considerable oedema of the parenchyma occurs, producing a firm enlargement of the affected region of the pancreas. If

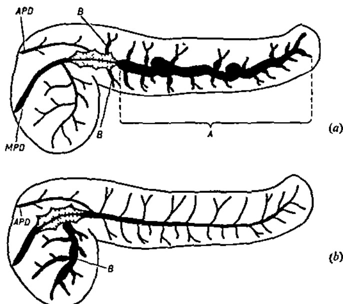


[illegible] Calcification in pan- [illegible]

the obstruction remains unrelieved this is followed by progressive atrophy and shrinkage of the organ. *The marked distention of the main* ducts which sometimes occurs is the result of the activity of numerous mucus-secreting glands in the wall of these channels. These glands undergo considerable hyperplasia when the main pancreatic ducts are obstructed so that these become distended by a turbid, glairy fluid, a process which bears close comparison with the accumulation of "white bile" *in the biliary passages in total biliary* obstruction. These tortuous, dilated ducts are often visible on the surface of the obstructed pancreas where they may be mistaken for cysts.

Morbid anatomy

Lesions due to ductal obstruction, which are sometimes termed "pancreatosis", present a remarkably constant morbid anatomical picture, modified to only a slight extent by the nature of the obstructing lesion, but increasing in intensity with its duration. Thus, after prolonged and complete blockage of the main duct and in the absence of any "safety valve" provided by an accessory channel, acinar atrophy becomes complete and the organ is reduced to a small, irregular fibrous remnant, containing a few dilated ducts, in which only the islets of Langerhans usually persist (Fig 16) A variable degree of infiltration with chronic inflammatory cells generally accompanies these changes Pancreatosis is most often encountered



by the surgeon in malignant disease of the pancreas, but it should be emphasized that these changes are entirely non-specific and follow obstruction from a number of causes They may therefore be seen as a pancreatic complication of calculous disease of the common bile duct, and are a common result of both primary pancreatic lithiasis and the later stages of relapsing pancreatitis.

Obstructive effects of malignant disease

The obstructive effects of malignant disease of the pancreas operate by two principal mechanisms (Fig. 15) The most marked change usually arises in the parts of the gland above the obstruction ("pancréatite d'amont"; Leger and Bréhant,

1956); thus in cases of carcinoma involving the main duct in the head of the pancreas, irregular parenchymal fibrous replacement and ductal dilatation frequently occur throughout the body and tail of the organ. The other type of lesion affects the tissue immediately overlying the growth itself and is the result of blockage of smaller ducts, so that replacement fibrosis predominates over ductal



Fig. 16 —Effects of complete ductal obstruction over many months. Pancreatic biopsy specimen from patient, aged 64 years, with obstructive jaundice and mass in head of pancreas. There is complete fibrous replacement of the acini, with scattered islets of Langerhans and ductal remnants Death 4 months later from pancreatic carcinoma, of which the sections gave no direct evidence. (Haematoxylin and eosin × 105.) (*By courtesy of the Editor of British Medical Journal.*)

dilatation. Both effects are extremely misleading to the surgeon and partially account for the common difficulty in obtaining histological confirmation by biopsy of the presence of malignancy in these patients. This confusion is increased by the tendency of pathologists to return a report of "chronic pancreatitis" upon material showing only non-specific lesions due to ductal obstruction

SURGICAL TREATMENT OF RELAPSING PANCREATITIS

Pre-operative clinical assessment

Surgical relief is required principally for the relief of the painful symptoms which trouble many of these patients, but may also be needed in duodenal or biliary obstruction and in the treatment of the various types of cyst which may result from the acute exacerbations. The diagnosis of chronic relapsing pancreatitis has already been discussed, but certain investigations are required before subjecting the patient to abdominal exploration. Full clinical assessment is followed by plain

abdominal radiography for pancreatic calcification; barium meal examination of the stomach and duodenum, and cholecystography with intravenous cholangiography A glucose tolerance curve is obtained. The more elaborate investigations requiring duodenal intubation are probably unnecessary as a routine and this applies also to attempts to provoke a rise in the serum amylase level by stimulation of pancreatic secretion

In most instances the clinical features are typical of relapsing pancreatitis, with pain as the presenting feature. But in cases in which the history is short and in which jaundice is present, it may be impossible to exclude malignant disease prior to laparotomy, even at which time it may, indeed, prove very difficult to establish the correct diagnosis. Apart from such cases, there is no urgency in subjecting the patient to operation, which should be an interval procedure carried out after full investigation and the correction, so far as possible, of any nutritional deficiencies which may exist Surgical intervention is not often required during the acute exacerbations

Choice of procedure

A confusing variety of surgical procedures has been advocated in the management of this disease This is to be explained partially by inexperience in a new field of surgical enterprise, and partially by our present lack of knowledge of the precise aetiology of many of these cases. Nevertheless, it is important to note that the disease is encountered in varying degrees of severity for which it is now clear that no single type of operation will be applicable. Moreover, in those advanced cases of the disease, in which severe parenchymal destruction, stone formation and ductal obstruction have developed, it is obvious that surgical relief can only be expected to follow the establishment of adequate drainage or the performance of radical excisional procedures which are often not justifiable. Fortunately, such patients are uncommon in Great Britain and surgery will more frequently be required for the earlier cases, in which reasonably satisfactory results can be expected in the control of the relapses, the relief of painful symptoms and the management of complications.

Surgical treatment may be considered under the following headings·

(1) Treatment of concomitant biliary disease.
(2) Biliary diversion in the early case
(3) Direct measures in the advanced case.
(4) Treatment of complications.

Treatment of concomitant biliary disease

There is abundant evidence that the successful surgical treatment of disease of the biliary tract results in relief of symptoms in the majority of patients in whom biliary and chronic pancreatic disease coexist (Thompson, Derrick and Howard, 1957) In most of these, however, it is clear that the symptoms are predominantly biliary in origin and that involvement of the pancreas is limited to obstructive and inflammatory change resulting from stones or infection in the common bile duct The frequency of such lesions is readily explained by the proximity of this channel to the main pancreatic duct, which can often be seen in pancreatograms in the living subject to descend parallel and very close to the bile duct, in the final 5–7

performed in 4 of these patients, 3 of whom obtained almost complete relief of symptoms over a period of 7 years In these patients, the procedure relieved both the intermittent biliary obstruction and the painful exacerbations of the pancreatitis. The patient in whom biliary diversion was unsuccessful finally succumbed to the effects of recurrent ascending cholangitis, which the operation failed to influence. Bowers (1956) has reported benefit in 16 of 17 patients with relapsing pancreatitis in whom he has used the operation. Choledocho-enterostomy may be performed by lateral anastomosis of the common duct to the duodenum or by division of the duct and reimplantation into the jejunum, the former procedure being most often used.

It should be remembered that both sphincterotomy and direct decompression of the common bile duct have the effect of producing a flaccid gall-bladder, prone to develop complications of biliary stasis, so that cholecystectomy should be an invariable step in the performance of either procedure

Direct measures in the advanced case

The patient with established and long-standing chronic relapsing pancreatitis presents with nutritional disturbance from parenchymal destruction, persistent and intractable pain from ductal obstruction or stones and may in addition have diabetes mellitus from islet insufficiency. It is impossible to influence the course of the disease in such cases by biliary diversion procedures; indeed, such patients are in a "burnt out" stage of the disease in which exacerbations of pancreatic necrosis rarely play a part, most of the secretory tissue having been destroyed. The surgical management of these patients with painful pancreatic insufficiency requires direct attack upon the pancreatic ducts, since, if drainage into the intestine can be re-established and stones removed, considerable parenchymal regeneration may accompany the resulting relief of symptoms The procedure to be adopted depends largely upon the findings at laparotomy, since involvement of the pancreas quite often affects localized segments of the organ. In determining the extent of the disease in such cases, operative pancreatography has probably its greatest application, since it allows the accurate demonstration of zones of ductal obstruction and the position of contained calculi

Operative pancreatography.—Although not essential in the surgical management of all cases of chronic pancreatic disease, this investigation is undoubtedly valuable in selected examples The precise technique is not of great importance. Doubilet (1956) recommended cannulation of the main pancreatic duct after sphincterotomy by the transduodenal approach, using a fine polythene cannula. His further step of passing the cannula back up the common bile duct, and bringing it to the exterior alongside a rubber T-tube placed in the common duct, appears to be seldom necessary Leger and Bréhant (1956) have pointed out that it is not usually necessary to divide the sphincter, since when this has been exposed by duodenotomy [illegible] atic duct in p [illegible] la, a small v [illegible] gently and slowly and the exposures made. The procedure carries little risk, provided care is taken to avoid extravasation of the medium

Retrograde pancreatography is carried out when indicated, by injecting the medium after amputation of the tip of the tail. When a free egress to the duodenum is demonstrated, the cut surface may be oversewn, but in cases where the channel is blocked it is necessary to implant the tail of the pancreas into the jejunum. This procedure is therefore usually only carried out as a step in the performance of caudal pancreatico-jejunostomy.

Indirect operative pancreatography is possible in many cases of relapsing pancreatitis, in most of which a "common channel" for bile and pancreatic secretions is present. The medium is injected into the common bile duct, but flows back up the pancreatic duct, enabling it to be demonstrated. This occurs in a higher proportion of patients after injection of 10 millilitres of N/10 hydrochloric acid into the duodenum, which produces marked spasm of the sphincter of Oddi.

(1) *Transduodenal pancreatolithotomy.*—This procedure is applicable in some cases of relapsing pancreatitis with stone formation, as well as in examples of primary pancreatic lithiasis. The duodenum is fully mobilized and opened and the sphincter of Oddi divided to expose the orifice of the main pancreatic duct, on the medial wall of the ampulla of Vater. This opening is then dilated to enable exploration of the main pancreatic duct, which may allow the extraction of calculi. It has been pointed out by Warren (1957), who has used the procedure in 31 patients, that the most usual initial site for the formation of stones lies within the terminal part of the main duct, within reach of the ampulla. Even when complete removal of the numerous small stones from the secondary ducts is impossible, it has been shown that disappearance of such calcification may follow removal of the larger stones and the re-establishment of efficient drainage into the duodenum. The transduodenal approach, when applicable, has the advantage that it entails little risk of the development of an external fistula, following closure of the anterior wall of the duodenum.

(2) *Caudal pancreatico-jejunostomy.*—When advanced disease of the head of the pancreas prevents the re-establishment of drainage into the duodenum, retrograde drainage of the pancreatic duct should be considered. The procedure is usually combined with splenectomy, after which the tail of the pancreas is amputated, the pancreatic duct cleared of stones and the remaining part of the body implanted in the end of a Roux loop of jejunum (Duval, 1956; Leger, 1958; Puestow and Gillesby, 1958)

(3) *Caudal pancreatectomy.*—A few instances have been described in which the disease has been limited to the distal part of the pancreas, so that it has proved possible to resect this region and, having established by pancreatography that the remaining portion of the pancreatic duct has an unobstructed course to the duodenum, to close the divided pancreas. The procedure is more often indicated for the removal of an area containing cysts than for other chronic lesions.

(4) *Pancreatico-duodenal resection.*—This hazardous undertaking may be considered the "last ditch" of a surgical attack on relapsing pancreatitis, since the disease process makes the operation technically much more difficult than when it is undertaken for carcinoma Indeed, it is seldom performed except on the mistaken diagnosis of malignant disease When the operation is carried out, the tail of the pancreas should be conserved and re-implanted into the intestine, to avoid the

dangerous metabolic state produced by total pancreatectomy (Longmire, Jordan and Briggs, 1956). In this respect it should again be emphasized that many of the changes of fibrosis and ductal dilatation encountered in the tail of the pancreas

prime importance in these patients.

Treatment of complications

The various conditions which may complicate the course of relapsing pancreatitis and require surgical relief include obstructive jaundice, duodenal obstruction, and pancreatic abscess, cyst, pseudocyst and fistula The detailed consideration of these is beyond the scope of the present review and their treatment follows recognized lines. With regard to the management of pancreatic cysts, large pseudocysts will in general be treated by external drainage in the first instance. Following the reduction in size it will be possible to carry out radiological investigation of the remnant by injection of opaque medium into the track and then plan further steps. Smaller cysts of the pancreas will be dealt with by excision or by internal drainage procedures, of which the simplest is generally anastomosis to the posterior wall of the stomach. Radiological investigation has great scope in the management of established pancreatic pseudocysts and fistulas by demonstrating their communication with the ductal system, since persistent discharge is unlikely to occur unless the normal route towards the duodenum is obstructed in some way. The resolution of pseudocysts even of large size after transduodenal sphincterotomy has recently been reported (Doubilet, 1957; Leger and Bréhant, 1956). The theoretical basis of the method is in the reduction of the unusually high secretory pressures (300 to

the duct system, this type of treatment will be uniformly ineffective in the case of cysts having no such communication. Published reports of the method have not all been favourable (Mallet-Guy and Michoulier, 1958) and further trial is required.

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ABSTRACTS RELATING TO THE ABDOMEN

PEPTIC ULCER OF THE STOMACH AND DUODENUM

Peptic ulcer

Mechanisms of activation after non-specific trauma

[illegible] of experiments in which a solution of phenol [illegible] e secretory and emptying [illegible] of the gastric contents. [illegible] When the subjects were [illegible] y rate or in the secretion [illegible] gave rise to a significant

increase in the concentration of acid and in the amount of pepsin and uropepsin The content of uropepsin was not an accurate indication as to the degree of gastric secretory activity. Changes in the gastric contents were not observed when histamine was injected before and after surgical intervention. The authors are of the opinion that peptic ulcera-

when the size of the ulcer increases. Cases are recorded in which these complications have occurred within a week after surgical or accidental trauma As yet it has not been possible to discover the nature of the stimulus which is responsible for gastric hypersecretion 12–14 hours after injury. In this respect neither histamine nor the Selye stress mechanism appears to be of importance Perhaps the anxiety and distress which accompany trauma may lead to vagal stimulation and hyperactivity of the cephalic phase. The effect is likely to be more pronounced when the gastric secretion is not buffered by food, saliva and regurgitation of the duodenal contents.

Association with tumours of the pancreas

OBERHELMAN, NELSEN and DRAGSTEDT (1958) described 2 cases of peptic ulcer associated with tumours of the pancreas and suggest that non-*beta* islet-cell pancreatic tumours may give rise to an ulcerogenic substance. The first patient was a man aged 52 years with a history of duodenal ulcer, perforation of the ulcer and massive gastro-intestinal haemorrhage Treatment included partial gastrectomy and transthoracic vagotomy. Subsequently a large perforated stomal ulcer was found during an exploratory laparotomy On further examination a carcinomatous lymphatic node was identified in the region of the head of the pancreas, whereupon the body and tail of the pancreas were removed. There was a further recurrence of the stomal ulcer and at another operation the duodenum and the remaining part of the pancreas were resected. After microscopical examination of the resected specimen it was concluded that a non-insulin-producing islet-cell tumour had arisen in ectopic pancreatic tissue situated in the duodenal wall near the duct of Santorini.

pancreatic tumour. Despite transabdominal vagotomy and posterior gastro-enterostomy for duodenal ulcer, the second patient, a man aged 37 years, died from massive haematemesis associated with a large stomal ulcer. At necropsy adenomas were detected in the pancreas and pituitary gland, the adrenal and parathyroid glands showed adenomatous hyperplasia and the head of the pancreas contained an islet-cell carcinoma. In contrast, no evidence of a pancreatic tumour was detected in a man, aged 64 years, with a recurrent marginal peptic ulcer and persistent gastric hypersecretion despite vagotomy and subtotal gastrectomy

Benign peptic ulceration

Results of total gastrectomy

BALINT and GUMMER (1958) reviewed the case histories of 12 patients who, since 1951, had had total gastrectomy for benign peptic ulcer at the Central Middlesex Hospital. There was no operative mortality While in 9 patients the operation was performed for

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oesophagoduodenal anastomoses were done for 2 patients, giving excellent results in one

while the other, who remained free of dyspeptic symptoms, contracted pulmonary tuberculosis 4 years and 4 months after operation. The creation of an artificial gastric reservoir from the jejunal loop was unsuccessful in the single case in which it was undertaken. The authors found that their results agreed with those where total gastrectomy had been performed at the same hospital for carcinoma. All 12 patients were given doses of intramuscular vitamin B_{12} and no instance of macrocytic anaemia had been found amongst them. Iron deficiency anaemia was liable to occur in the same way as in patients undergoing partial gastrectomy and this could be corrected by oral iron. The authors concluded that total gastrectomy with a Roux-en-Y reconstruction is a justifiable operation for patients with anastomotic ulceration not cured by adequate partial gastrectomy and vagotomy, as well as in patients with simple gastric ulcer suspected of being malignant at the time of operation in whom subtotal resection would not have given adequate clearance.

Gastric ulcers in the cardiac region

Surgical treatment

WALLENSTEN (1958) reported on 40 cases, 28 men and 12 women, of gastric ulcer in the vicinity of the cardia treated surgically in the Surgical Department of Serafimerlasarettet between 1934 and 1956. All but two patients were over 40 years of age and all had ulcers either in the cardia or on the lesser curvature within 3 centimetres of it, the distance being measured at operation. In 11 patients a history of less than one year's duration made it difficult to exclude the possibility of a cancerous ulcer. Apart from two cases in which total gastrectomy, and resection of the upper part of the stomach with oesophagogastrostomy were performed respectively, the operative method chosen was ... were 5 ... haemorr- ... of death ... x, acute ... embolus. In one case reoperation was necessary because of ...

In view of the freedom from symptoms after operation he prefers radical surgery to vagotomy or the so-called palliative gastric resection described by Kelling-Madlener.

Gastric ulcer and cancer

... f surgery in the treatment of gastric ulcer, JORDAN ... controlled medical treatment it is possible to dis- ... be benign. The ... recurrence of ulceration should be regarded ... malignant ... lies. Cells ... 5 per cent with the appropriate microscopical tests. Some clinicians suspect ... there is a short history of atypical or unremitting symptoms or if histamine-fast achlorhydria is detected. The radiologist attaches importance to an irregular appearance of the crater, failure to observe folds radiating towards the crater, the presence of a meniscus and local rigidity of the gastric wall. In attempting to control precipitating factors, it is ...

The basic principle is to rest the stomach and neutralize the gastric acidity. The Sippy

performed immediately after the initial examination.

Duodenal ulcer

Rationale of selective surgery

BRUCE and his colleagues (1959) studied the relationship between recurrent jejunal

secretion of the gastric remnant was higher than that of an intact normal stomach.

surgical procedure should be made after the augmented histamine test Patients with

a more satisfactory procedure.

Postbulbar duodenal ulceration

COOKE and HUTTON (1958) studied 25 cases (23 males and 2 females) of postbulbar duodenal ulceration They defined postbulbar duodenal ulcers as all those arising in the duodenum beyond the bulb, although they are mainly concerned with those in the immediate postbulbar area. They consider that the diagnosis was often missed, owing to the ulcer remaining undiscovered both by barium meal examination and at laparotomy, with the result that this severe and even fatal disability might be regarded as neurotic.

groups of patients: in the firs
with a long history of pain ar
mittent obstructive group, the
of profuse vomiting and severe
They conclude that medical treatment is usually unsatisfactory and that operation, although technically difficult, is indicated in most cases.

Bleeding duodenal ulcer

Vagotomy and pyloroplasty

SMITH and FARRIS (1959) advocated the use of vagotomy and pyloroplasty in the management of duodenal ulcer associated with haemorrhage. Care must be taken to interrupt all vagal pathway
phageal wall In cases of
duodenostomy with immec
inflammation and oedema r
should be employed, with

of 3 years the authors operated upon 21 patients suffering from duodenal ulcer and haemorrhage. In 7 cases massive bleeding was a prominent feature. Every patient recovered and there were no cases of post-operative haemorrhage or recurrent ulceration. The series included a man, aged 69 years, who was given blood transfusions for

recurred. A similar technique was adopted in the management of a patient with duodenal ulceration, cirrhosis of the liver and a considerable loss of blood in the stools. Operation revealed a posterior duodenal ulcer with perforation into the pancreas and an extruding artery. The patient continued to be free from symptoms for 16 months after surgical treatment. It is pointed out that abnormal phases of gastric hypersecretion may be effectively modified by vagotomy combined with subtotal gastrectomy, gastro-enterostomy or pyloroplasty

Follow-up study

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December 1952 catalogued under designations such as "duodenal ulcer" and "gastro-intestinal haemorrhage". After excluding 6 cases lost to follow-up study, the remainder were observed for an average period of 85 months. As might have been expected in a Veterans Administration Hospital, all but one of the 136 patients were males, their ages ranging from 20 to 79 years; 8 (5 9 per cent) died from gastro-intestinal haemorrhage, all being over 50 years of age. Recurrent bleeding within a 5-year period occurred in approximately 40 per cent of patients not subjected to operation It appeared to be higher in patients who had already had two or more haemorrhages than in those with only one haemorrhage. After subtotal gastrectomy, performed primarily for gastro-intestinal bleeding, there was a significant occurrence of further haemorrhage, this being noted in 10 out of 48 patients (approximately 20 per cent), within 5 years of operation. Bleeding after subtotal gastrectomy was particularly frequent in the 12 patients who were operated upon because of continued uncontrolled haemorrhage. The authors concluded that although subtotal gastrectomy seemed to reduce the frequency of recurrent bleeding in patients with duodenal ulcer, in those in whom it was severe pre-operatively there was quite a likelihood of equally severe recurrent post-operative bleeding. They also noted that gastro-intestinal symptoms were as frequent in those operated on as in those not treated surgically.

Gastrojejunal ulcer

Radiographic examination

Ellis (1958) discussed the technique of x-ray examination in cases of gastrojejunal

Intubation may prove to be helpful in the examination of the stoma and afferent jejunal loop. A barium enema is required when the presence of a gastrojejunocolic fistula is suspected. After partial gastrectomy for duodenal ulcer routine x-ray examination of the upper part of the gastro-intestinal tract is not considered to be essential if the patient is

78 cases the ulcer developed after simple gastrojejunostomy and in the remaining cases after partial gastrectomy. The ulcers were identified radiologically in 44 and 45 cases, respectively.

Anastomotic ulcer

Management

Balint and his colleagues (1957) pointed out that anastomotic ulceration develops in 3–5 per cent of patients after partial gastrectomy for duodenal ulcer. The percentage is greater after gastro-enterostomy Radiological findings may be negative despite the presence of anastomotic ulceration. It is recommended that vagotomy and partial gastrectomy should be performed in cases of anastomotic ulcer associated with gastro-enterostomy. If the ulcer develops after partial gastrectomy abdominal vagotomy is the treatment of choice Revision of the anastomosis may be required and it may be necessary to remove the ulcer by means of a limited gastric resection. Total gastrectomy is recommended in cases of persistent recurrence of ulceration. There should be no delay in performing this operation if anastomotic ulcers recur after vagotomy and gastrectomy. The authors base their recommendations upon the findings in 146 men and 14 women with an average age of 46 years Nineteen deaths were recorded, including 4 due to haemorrhage and other complications of the anastomotic ulcer. Medical treatment was employed in 42 cases, but the treatment was almost invariably of little avail Partial gastrectomy was employed in 38 cases, and there were 9 recurrences in this group. Radical partial gastrectomy was selected for the treatment of 28 patients No recurrences were encountered but the results were unsatisfactory, so far as symptoms were concerned. Recurrent ulceration took place in 9 of 20 cases when further partial gastrectomy was performed after an initial partial gastrectomy Only 4 recurrences were encountered, however, in 27 patients who were treated by abdominal vagotomy combined in some instances with revision of the anastomosis One recurrence only was found in 11 patients after vagotomy and a limited gastric resection.

PANCREATITIS

Pancreatic disease

Diagnosis

Marks and Tompsett (1958) point out that owing to the large functional reserve of the pancreas overt signs of deficiency do not readily occur. A clinical diagnosis of pancreatic disease depends upon the use of laboratory procedures such as examination of

the urine and faeces, of serum enzyme

the production of enzyme only. The response to secretin stimulation persists for at least 80 minutes, but after the injection of pancreozymin the response is complete within 20 minutes. After obtaining an alkaline fasting duodenal aspirate the authors injected secretin. One hour later a preparation of pancreozymin was administered. The authors describe a new technique for testing pancreatic function. A Levin tube with a small mercury-loaded bag is passed into the stomach

nasal tube is then passed into the stomach for separate but simultaneous collection of gastric juice. The activity of amylase, trypsin and lipase in the duodenal fluid was measured. When these tests

response a

Abnormal

in 7 of 9 tests performed on patients with possible but unproven pancreatic disorder. Provided duodenal aspiration was satisfactory

persistent steatorrhoea. Oral glucose-tolerance tests were of assistance in differentiating between pancreatic and non-pancreatic steatorrhoea. Provocative serum-amylase tests gave positive results in 4 of 16 cases of proven pancreatic disease. Reproduction of abdominal pain after the administration of secretin and morphine was considered to be unnecessary for routine use.

Chronic relapsing pancreatitis

Retrograde surgical drainage of the pancreas

PUESTOW and GILLESBY (1958) discuss the basic principles which must be understood in order to determine the correct management of chronic relapsing pancreatitis. In this disease, they believe the pain to be due to partial obstruction of the ducts. The obstruction may be multiple, producing a "chain of lakes" appearance of the ducts on pancreatography. Accumulation of mucoid material at the site of strictures may contribute to the blockage. The authors believe that since pancreatic calcification is not confined to the ducts, its surgical removal is unlikely to relieve ductal obstruction. Adequate drainage may result in regeneration of pancreatic tissue as well as the relief of pain. This may be achieved by caudal pancreatico-jejunostomy, which the authors have carried out in 21 patients without mortality. Various methods were used, but a modification which ensured drainage of a long segment of the pancreatic duct gave best results. In the technique described the spleen is removed and the tail of the pancreas mobilized and transected. The main duct is then slit open over a probe and the opening continued as far towards the right as possible. The anastomosis is made either by slipping the jejunum over the opened pancreas or by a lateral anastomosis; this is followed by a Roux-Y reconstruction of the intestine. Pancreatico-gastrostomy was performed on two occasions. The results in

pain returned in a further

the authors' method,

Sphincteroplasty for recurrent pancreatitis

JONES, SMITH and GREGORY (1958) believe that constriction of the pancreatic duct

duodenal wall, after it has been exposed by anterior duodenotomy. By suturing the adjacent cut edges of the common duct and duodenal wall, a stoma 2–3 centimetres long is produced. The authors have used transduodenal sphincteroplasty in 28 patients with recurrent pancreatitis The series comprises 17 males and 11 females, aged 27–81 years. Symptoms and signs included nausea and vomiting, upper abdominal pain with typical

of the common bile duct A post-operative study of 25 patients showed that sphinctero-plasty had been successful in preventing recurrence of the pancreatitis in 19, but 6 developed further attacks. Cholangiography, combined with intravenous injection of morphine sulphate, indicated that the operation had successfully eliminated the con-

following sphincteroplasty. The procedure is not recommended in the presence of intra-pancreatic ductal obstruction, in which caudal pancreatectomy with retrograde drainage is advised. Similarly, in segmental disease of the pancreas and when destruction is advanced, excisional procedures should be considered.

Pancreatic pseudocyst

Clinical and surgical aspects

Noteworthy radiological signs were the presence of pancreatic calcification in 9 patients; others showed displacement of the stomach and widening of the duodenal loop The

a further 2 patients

Acute pancreatitis with peritoneal fat necrosis

Radiological diagnosis

MERNER (1958) describes 2 cases of severe acute pancreatic necrosis in which intra-abdominal fat necrosis
an obese woman, aged 5
and cholelithiasis A ch
bladder Skiagrams sho
abdomen These shadows proved at laparotomy to be due to islands of calcium soaps in areas of fat
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hours.
in the

densities disseminated throughout the abdomen which were interpreted as the result of fat necrosis accompanying acute pancreatitis. The diagnosis of cholelithiasis and acute pancreatitis was confirmed at laparotomy. Subsequently, a pseudocyst developed and the patient later suffered a fatal haematemesis. The illness was severe in both patients since they developed haemorrhagic peritoneal fluid and inflammatory lesions of the lungs and pleura. Merner points out that in cases of fulminating pancreatitis serial skiagrams may show evidence of lipoid necrosis several hours after the onset of the disease.

Pancreatoduodenal resection

CRAIGHEAD and LIEN (1958) hold that the chances of long-term survival after pancreato-duodenectomy are by no means negligible. However, their review of the records of 78 patients undergoing this operation allows little optimism. The resection included the entire pancreas together with the duodenum in 13 cases, with 8 deaths. No patient survived this procedure beyond 1 year, a mortality to which the serious diabetic state produced by total pancreatectomy largely contributed. Partial pancreatectomy was performed in 65 patients, of whom 33 died. The overall hospital mortality of these two procedures was therefore 53 per cent The operation was performed for carcinoma of the pancreas in 50 patients, of whom only 2 survived more than 5 years. Fifteen partial resections for ampullary carcinoma produced two 5-year survivals, with a further 6 patients remaining free from recurrence during a shorter period One patient with duodenal carcinoma survived 5 years These 5 patients living beyond 5 years were the only survivors from 72 pancreato-duodenal resections performed for malignant disease. They include, however, survivals of 8 and 9 years in 2 patients.

Hyperparathyroidism and acute pancreatitis

HOAR and GORLIN (1958) described a case of hyperparathyroidism presenting with symptoms of acute pancreatitis A woman, aged 74 years, had an attack of abdominal pain, loose stools and pyrexia The pain was situated in the right upper quadrant of the abdomen and near the umbilicus. Serum examination showed an increased amylase content with a rise in the serum calcium. A cholecystogram showed lack of function of the gall-bladder Skiagrams of the skeletal system revealed slight rarefaction of the bones and absorption of cortical bone in a phalanx. After the abdominal pain had subsided, mental confusion became prominent. On the sixteenth day of the illness a large adenoma of the left inferior parathyroid gland was removed. In spite of the presence of severe ischaemic heart disease the patient made a complete recovery. The authors point out that the secretion of excessive amounts of parathormone may cause focal pancreatic necrosis. Furthermore, when the serum calcium is increased, calcium salts may be precipitated in the pancreatic ducts, causing obstruction.

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RECTUM AND ANUS

CRITICAL REVIEW OF RECTAL SURGERY

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It is customary to regard rectal surgery as one of the longer established and now relatively static branches of surgery. Certainly when viewed alongside cardiac and peripheral vascular surgery, which have evolved so dramatically in the past decade or so, it does appear comparatively stationary. But since the original section of *British Surgical Practice*, Vol 7, dealing with the surgery of the rectum was published in 1950 there have been a number of innovations in this field, two or three of which must be classed as major advances and several others as significant, if lesser, improvements. In this chapter it is proposed to survey these new conceptions and see to what extent they have modified the contemporary practice of rectal surgery.

IMMEDIATE SKIN COVER IN MINOR RECTAL SURGERY

One of the first principles of so-called minor rectal—really anal—surgery has hitherto been that sepsis is inevitable in this region and that anal wounds must be so managed that they can resist infection and proceed to satisfactory healing despite it. This in effect has meant laying the wounds widely open at the time of operation and keeping them open subsequently by suitably applied dressings so that they fill from the depths with granulations, which eventually become covered by epithelium growing from the periphery. This principle goes back several hundreds of years, indeed to antiquity, and it is clearly described in the writings of John Arderne, a 14th-century surgeon (*see* D'Arcy Power, 1910). But it is probably correct to say that the modern, more radical version of this technique with free excision of the skin edges to give a wide guttered or saucerized wound has been popularized mainly by the teaching of the surgeons at St. Mark's Hospital over the past 30 or more years.

Reliable healing by second intention can be obtained by this method, if carefully applied, in the treatment of haemorrhoids, fissures and, above all, fistulae. Indeed there are few fistulae that cannot be successfully treated along these lines. There are, however, several obvious disadvantages in leaving anal wounds open to

granulate. First, there is the length of time required for complete healing to take place, and with a large horse-shoe fistula this may amount to 2 or 3 months, and even with a low fistula or anal fissure is seldom less than 4 or 5 weeks. Secondly, there is the not inconsiderable discomfort from the large raw area, which during the initial week or two after operation may occasion a great deal of pain, not lightly to be dismissed by the patient. And thirdly, the scarring that inevitably follows healing by granulation may lead to troublesome stenosis if special precautions are not observed, sometimes indeed despite such measures. As against the complete reliability of healing which this method affords, these inconveniences must be rated as relatively unimportant, but in the present antibiotic era, when potent antibacterial substances are available for systemic and enteral use, it is appropriate to ask whether sepsis and healing by granulation must still remain the hallmarks of minor rectal surgery. Is primary skin cover still an unattainable ideal in this situation? In the past decade attempts have been made to answer that question in the negative by utilizing primary suture or immediate skin grafting of ano-rectal wounds.

Primary suture

Primary suture of wounds after excision of anal fistulae was warmly recommended in selected cases by Tuttle (1903) many years ago In the application of this technique he emphasized that special care must be taken to remove the fistulous track completely and to bring the walls of the wound into firm apposition by buried sutures But the method never became popular, presumably because it seemed unsound in theory or the results were found to be unsatisfactory in practice, and suture of fistula wounds has been universally condemned or ignored by authorities such as Gabriel (1948), Goodsall and Miles (1900) and Milligan and his colleagues (1948).

More recently Starr (1953, 1959) of Sydney has revived this method of dealing with fistula and fissure wounds, employing sulphonamides or antibiotics for bowel antisepsis and systemic use before and after operation; he claims to have been invariably successful in securing uneventful primary union.

Stimulated by Starr's experiences the author has also practised primary suture in a few patients with what appeared to be specially suitable wounds following the laying open of low anal fistulae Particular care was taken to excise the fistula in its entirety and leave fresh supple raw surfaces which were then apposed by two or more layers of buried fine, plain, catgut sutures Finally the skin was coapted with Michel clips or silk sutures and any part of the anal lining implicated in the wound sutured with catgut stitches. Antibiotics were used for intestinal antisepsis and systemic chemotherapy in all instances. Of 20 cases treated in this way 12 secured uncomplicated primary healing, but in 7 the wounds became infected and had to be laid open to heal by granulation. There is no doubt from these results that while primary union can sometimes be achieved by this technique, the proportion of successes is too small to make it a practicable method for routine use, even in apparently favourable cases.

In regard to the small external anal wounds resulting from haemorrhoidectomy, though Lockhart-Mummery (1934) favoured closing these to some extent by

suturing the skin edges to the ligatures on the main pile pedicles, the consensus of surgical opinion in Great Britain at the present time is that they should be left widely open to granulate. American surgeons such as Buie (1932), David (1949) and Ferguson (1957), however, advocated partial or complete suture of these wounds, as has Starr (1959), but it is difficult to judge from their writings how successful this practice is in securing primary union. Such sutured wounds look very tidy in the theatre at the conclusion of the operation, and even more so as depicted by the medical artist, but the result 5 to 7 days later in the present writer's experience is apt to be bitterly disappointing. For a period in 1947–1948 under cover of colon antisepsis with Sulphathalidine and systemic chemotherapy with penicillin, the author employed routinely for haemorrhoidectomy Mitchell's (1903) method of clamping and overstitching, and closed the external wounds completely with catgut sutures. Most of these wounds became to some extent infected and underwent partial or complete separation. Moreover, in their inflamed and oedematous condition they were, apparently, more painful than the open wounds usually left after haemorrhoidectomy. Further, the ultimate end-results were less satisfactory after primary suture in that anal skin tags tended to be less thoroughly removed than with the open technique because of the desire to facilitate apposition of the edges of the skin wounds. As a result of these experiences the author has come to the conclusion that haemorrhoidectomy wounds are better left open to granulate than sutured.

Probably the most promising use of primary suture in the anal region has surprisingly been in connexion with perianal and ischio-rectal abscesses. It is clear from the work of Ellis (*see* chapter "Progress in the Casualty Department") that [illegible] it is now possible to [illegible] by curettage of the [illegible]bability of securing primary union. The fact that this method can be applied as an outpatient procedure confers considerable advantages which outweigh the disadvantage that a small percentage of the cases so treated develop a fistula-in-ano requiring subsequent operative treatment. It is probable that one reason why these sutured wounds do relatively so well is that the incision usually lies outside the anal verge and does not extend into the anal canal itself.

Split-skin grafting

Secondary Thiersch grafting was introduced into ano-rectal surgery by Gabriel in 1927, the grafts being applied to the granulating surfaces once the crevices and irregularities had evened out. However, the method never became popular mainly because of the low percentage of successful "takes". *Primary Thiersch grafting* was apparently first used in this region by Rank (1944) of Melbourne who employed it to cover wounds resulting from the excision of pilonidal sinuses. In 1953 Hughes, also of Melbourne, applied primary grafting to anal wounds proper, for example, after laying open fistulae or excising fissures. In certain instances where there was too much initial oozing of serum and blood from large deep wounds to permit of the immediate use of grafts Hughes has recommended *delayed primary grafting* 2 or 3 days later, the wound meanwhile being packed with dry gauze. The grafts

are taken from the medial aspect of the thigh and applied as sheets to the raw surface; they are sutured to one another and to the skin edges to provide a complete covering. The grafts may be snicked with scissors at many points to facilitate the escape of serous fluid and prevent them being "floated off". Finally, a pack of cotton wool soaked in flavine, or a pad of sponge rubber, is applied to the graft and fixed in position by tying over it to one another the tails of the stitches uniting the graft to the skin (Fig. 19). In this way the graft is firmly compressed against the raw surface of the wound. Fixation and compression of the grafts are further enhanced by a generous pad of gauze and wool held in position by strapping extending across both buttocks. As the grafting is only carried out as the final step in a formal fistula operation (or excision of fissure) the area to which it is applied is roughly concave or guttered, and in the case of high posterior horseshoe fistulae, may be a very deep furrow indeed. Firm pressure by a moulded pack is therefore essential if good apposition is to be secured. The pack is retained in position for 5 or 6 days, the sutures are then removed and the bowels opened by an enema or aperient. The healing of any remaining raw areas is completed under a regime of baths, irrigations and eusol dressings as required.

The results claimed by Hughes (1953) have been most impressive—40 cases treated by grafting, with virtually complete "takes" in 30, and substantial, though incomplete, "takes" in most of the others. The present writer's results with primary Thiersch grafting in 22 cases, mostly with low anal fistula wounds, have been much less satisfactory; of the 22 cases only 13 secured complete or nearly complete "takes", and 4, 50–70 per cent "takes" In addition 4 or 5 of his patients complained bitterly of pain in the donor site on the thigh and a few found the period of confinement of the bowels irksome and uncomfortable But an important point is that none of them suffered any harm from the grafting for if it did not take, the patient was left with an open wound well designed to heal by second intention.

Advantages

The advantages of primary grafting in the anal region, if it is completely successful, need no emphasis, for the patient leaves hospital in 10–14 days with a healed wound instead of having to spend several weeks in hospital having dressings and to continue with this regime for some time after discharge. And yet the method has not so far found much favour, mainly because of the operative time necessary to prepare the grafts and fix them in position; with a small fistula wound this will usually amount to nearly an hour, and with a large horseshoe wound to 2 or 3 hours. This tempo accords ill with the rapid "cut and thrust" of much minor rectal surgery. Moreover, these cases tend to come at the end of the surgeon's operating list when he may already have done 2 or 3 major abdominal or abdomino-perineal operations requiring altogether several hours; he is unlikely to relish a fistula operation at this stage which requires another 2 or 3 hours' operating time. It only needs one or two unsuccessful experiences with grafting—and the results are somewhat unpredictable—to convince him that there are more profitable uses of valuable theatre time. This is unfortunate because with increasing experience the steps necessary to fix the grafts can be expedited, and the method can be made to afford more reliable results, but the unpredictability of the outcome with grafting will probably always militate against its use.

ANAL FISSURE

Anal fissure has attracted much attention in the last few years. As a result new methods of treatment have been evolved and, in the process, fresh light has been thrown on the anatomy of the anal region necessitating to some extent a recasting of our ideas on the subject. The conception of anal anatomy that had previously guided most surgeons was that formulated by Milligan and Morgan in their classical papers in the mid-1930's. Much of their teaching is portrayed in their well known diagram of a section of the anal canal (Fig. 17A). According to them the external sphincter was composed of three separate parts, the subcutaneous, *superficial and deep portions* respectively. The *subcutaneous external sphincter* was alleged by Blaisdell (1937), Gabriel (1948), Milligan (1943) and many others to bear a close aetiological relationship to fissure-in-ano. According to them the fissure lay on this part of the external sphincter; it was fibres of this muscle that were frequently exposed in the floor of the fissure; and the spasm of the anus

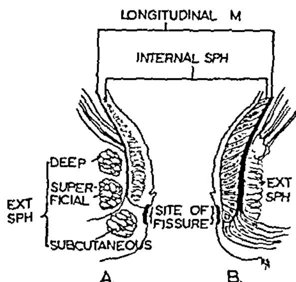


FIG. 17.—Old and new ideas of anal anatomy: (A) the Milligan - Morgan doctrine; (B) the newer conception.

regularly found *in conjunction with a fissure* was due mainly to contraction of this muscle (Fig. 17A). They *believed* that division of the subcutaneous external sphincter was an essential item in the surgical treatment of fissure-in-ano.

This doctrine was accepted without question till 1951 when Eisenhammer (1951, 1953) of Johannesburg claimed that the important *muscle in* regard to anal fissure is not the subcutaneous external sphincter *but the internal* sphincter. He *showed* that the fissure ordinarily lays on the *lower third* of this muscle and could be successfully treated by a simple *internal sphincterotomy*. These conclusions were [illegible] confirmed by further dissections and operative studies by Goligher, [illegible]

more than the rather prominent lower [illegible] internal anal sphincter.

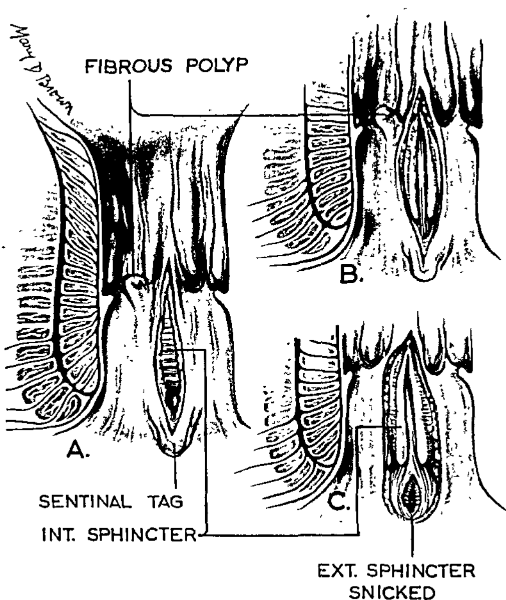


FIG 18 —(A) Posterior fissure-in-ano with polyp and skin tag ; (B) *internal sphincter muscle* partly divided, (C) internal sphincter muscle divided exposing underlying longitudinal muscle sheet. Skin tag and polyp removed.

Internal sphincterotomy has one great advantage over Gabriel's (1930) method of excision of the fissure with a triangle of perianal skin and partial division of the sphincter—it can be performed as an outpatient procedure under local anaesthesia (inferior haemorrhoidal block) or at most need only detain the patient for 2 or 3 days in hospital. Its acceptance in Great Britain has owed a good deal to the advocacy of H. R. Thompson of St Mark's Hospital, and Morgan and Thompson (1956) give a clear account of its technique. Full operative details are also given by Goligher (1959*b*) and Lockhart-Mummery (1957). Two instruments are essential for its easy performance—a bivalve speculum, either a modified Ricord or the author's pattern, and a long No. 7 Bard-Parker handle mounted with a small No. 10 blade. The operation can be carried out in the left lateral or lithotomy position as preferred An incision is made from the pectinate line to just outside the anal margin and deepened through the internal sphincter till the intersphincteric plane is

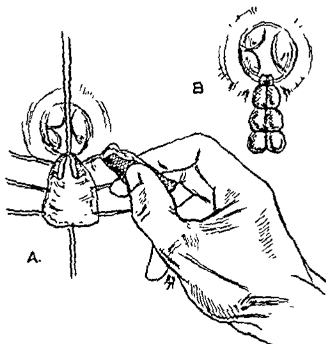


Fig. 19.—(A) A mould is made of tulle gras and wool, over the face of the mould is laid the split skin graft. The mould with graft is placed in the wound. (B) The graft is secured by tying the guy sutures across the back of the mould.

reached (Fig 18) The external sphincter may be snicked slightly at the lower end of the incision The use of gauze swabs soaked in 1 per 1,000 liquor adrenaline is of great help in securing a bloodless field and defining the anatomy with accuracy. The skin tag at the lower end and the fibrous polyp at the upper end of the wound are excised. Finally a eusol gauze dressing is applied to the anus, a corner being tucked into the canal in relation to the wound.

The patient returns to bed and is sedated with codeine; in addition 100 milligrams of pethidine are prescribed for the first night. The bowels are opened with a mild aperient on the second or third day, and usually a relatively painless motion results. Though the immediate relief of pain is a striking feature as a rule after this operation, the wound often takes 3 or 4 weeks to heal and sometimes remains in an unhealed condition for even longer. More recently the present writer has been

carrying out the sphincterotomy not in the midline posteriorly but in the postero-lateral position as recommended by Eisenhammer (1951, 1953) and originally practised by Miles (1939) in his pectenotomy operation. His impression is that in this situation more rapid healing results. Slight insecurity for flatus or liquid faeces is very occasionally experienced after internal sphincterotomy, when the division of muscle is carried up to the ano-rectal ring, but this invariably corrects itself within a week or so of the operation, and no permanent impairment of anal function ever results.

Excision of anal fissure and immediate skin graft

Hughes (1953) has sought to eliminate the main disadvantage of Gabriel's triangular excision of anal fissure, namely, the length of the convalescence in hospital, by applying an immediate Thiersch graft to the raw area at the conclusion of the operation as in Fig. 19 (A and B) He claimed that the graft almost invariably "takes" in its entirety and the patient leaves hospital in 7–10 days with a completely healed wound. This is a considerable improvement on the results of Gabriel's operation in its original form, but it still means a much longer stay in hospital than after a simple internal sphincterotomy. This fact, together with the much greater intricacy of a grafting operation, have combined to prevent Hughes' method becoming popular in Great Britain.

INTERNAL HAEMORRHOIDS

A new technique for submucosal haemorrhoidectomy with high ligation

Of the three main methods of removing internal piles—ligature and excision, clamping and cauterization and clamping and overstitching—the ligature and excision operation is probably the one most favoured in Britain at the present day It was the technique advocated by Frederick Salmon, the founder of St Mark's Hospital. As practised by him it was a high ligation, the internal pile being separated from the skin by a cut at the mucocutaneous junction and stripped up to the ano-rectal junction where the main ligature was applied. This had the advantage that it provided a very thorough removal of the haemorrhoid, but it suffered the drawback that it left considerable raw areas which were liable, as they healed, to produce stricturing of the anal canal To avoid this risk Miles (1919) and later Milligan and his colleagues (1937) developed the technique of low ligation in which the initial cut was made in the perianal skin up to the mucocutaneous junction and the piles were drawn forcibly downwards so that the pile pedicle could be tied at the level of the lower border of the internal sphincter. Provided that adequate bridges of skin and mucosa were left between the three main piles this operation largely avoided the complication of stricture.

Parks (1956) has criticized this technique on the score that it is associated with a fair amount of post-operative pain owing to inclusion of the anal mucosa in the ligatures. He has therefore elaborated a method of performing a submucous haemorrhoidectomy based on the technique originally described by Cooper (1809) and Petit (1774) A special bivalve retractor is necessary to separate the anal margins The principle of the operation is to incise the mucosa and skin longitudinally over each pile in turn and raise two skin and mucosal flaps, thus exposing

the essential vascular part of the pile. Starting at the lower end the haemorrhoid is then dissected free from the underlying structures and stripped up to its superior pedicle which is ligated at the ano-rectal ring. The mucosal and skin flaps, suitably trimmed at the anal orifice to remove redundant tags, fall back on the raw surfaces and give them almost complete epithelial cover, which is rapidly completed by the healing process. The value of injecting a solution containing adrenaline into the submucous tissues to reduce the amount of bleeding during the turning up of the flaps is emphasized

The claims made for this operation are that it is followed by much less pain than is the Milligan-Morgan method because the mucosa is not included in the main ligatures, and that it is even more effective in avoiding post-operative stricture formation because of the preservation of flaps of mucosa and skin. Parks (1956) has used it on over 50 patients with encouraging results, though he admits to recurrences within 1 year in 12 per cent of his cases. This is certainly an interesting technical innovation. It might be thought that the reflection of the mucosa flaps would present difficulties if haemorrhage from the closely related submucosal veins was to be avoided. The secret of success in this manoeuvre is to infiltrate very large amounts of the adrenaline solution into the submucosa—up to 40 millilitres for each pile mass. If this operation is found to diminish the amount of pain normally associated with haemorrhoidectomy, as claimed by Parks, it will be a considerable advance, but it is notoriously difficult to compare reliably the amount of pain produced by different operative procedures. The present writer's experience of 25–30 cases treated by submucous haemorrhoidectomy has failed to convince him that there is any significant difference in the amount of post-operative pain as compared with that after the standard ligature and excision operation, though obviously a more extensive trial would be necessary to do the operation justice. As for post-operative stricture, this is already a very infrequent complication after the Milligan-Morgan type of operation so that it is difficult to see how this new technique could enjoy any real advantage in this respect Undoubtedly submucous haemorrhoidectomy is technically far from easy and in the author's hands usually takes about an hour to do

COMPLETE PROLAPSE OF THE RECTUM

Ten years ago the most popular operation in Great Britain for complete rectal prolapse was *amputation of the prolapse or recto-sigmoidectomy done entirely from below* In 1949 the careful analysis by Hughes of the collective series of 150 cases treated by this operation at St. Mark's Hospital during the previous 18 years showed that *there was a 60 per cent recurrence rate* and that over half the successful patients were incontinent. The poor functional results were attributed [illegible]

that is followed by such frequent recurrence [illegible] and during the past *decade most surgeons have turned their* attentions to other operations in the treatment of complete rectal prolapse, particularly to those

conducted wholly or partly from the abdominal aspect. There has been no dearth of surgical methods to choose from, but surgical fashion in the British Commonwealth has apparently settled mainly on two operations—anterior resection and a modification of the Roscoe Graham or Dunphy type of repair.

Anterior resection

This operation was first applied to the treatment of complete rectal prolapse by Muir (1955, 1956) of King's College Hospital. It suffices to say here that the operation is performed in a very similar manner to a low anterior resection for rectal carcinoma. Muir emphasized the importance of an extensive mobilization of the rectum down to the ano-rectal ring with exposure of the junction of the rectum and the levator muscles laterally and posteriorly. Anteriorly the deep pouch of Douglas is dissected off the posterior vaginal wall and excised. The rectum is divided across leaving a 3-inch stump, and sufficient sigmoid colon is resected along with the upper rectum to remove any unnecessary "slack". When the anastomosis is completed the pelvic peritoneum is stripped off the back of the uterus and broad ligaments and sutured as high as possible on the front of the sacrum and the colon so as to leave no pouch of Douglas.

Anterior resection has been performed by Muir (1959) on 34 patients with complete rectal prolapse in the last 10 years with one death and no recurrences to date, and many other surgeons including the present writer have also found it a satisfactory method It is presumably effective in two ways—by removing all redundant bowel in the recto-sigmoid region, and by causing extensive adhesions around the rectum which fix it to its bed, and especially anchor the anastomosis to the front of the sacrum.

The modified Roscoe Graham or Dunphy type of repair

There are good grounds for believing that complete rectal prolapse is really a herniation of the pouch of Douglas into the rectum and thence through the anus (Fig. 20) Its logical treatment, therefore, would seem to involve elimination of the especially deep peritoneal pouch present in these cases, strengthening of the pelvic floor and narrowing of the ano-rectal ring. These are the objectives of the Roscoe Graham operation, so that in theory it is an eminently sound procedure for this condition In practice, however, most surgeons have found it difficult to achieve a satisfactory suture of the pelvic floor entirely from above by the technique described by Graham (1942) Consequently, combined perineo-abdominal or abdomino-perineal modifications of the operation have been introduced with or without resection of part of the rectum (Brintnall, 1952; Butler, 1952; Dunphy, 1948; Hughes, Gleadell and Turner, 1957; Newell, 1954). As Goligher (1958*a*) has recently shown, however, these more elaborate methods are not really necessary, for a perfectly adequate repair can be conducted entirely from the abdominal aspect if a suitable technique is employed This involves a more extensive dissection and mobilization of the rectum than was originally recommended by Graham (1942).

The operation is performed with the patient in a fairly steep Trendelenburg position The iliac colon and mesocolon are freed by dividing any developmental

adhesions to the parietal peritoneum of the left iliac fossa. The pelvic peritoneum is then divided with scissors along the brim of the pelvis on either side, the two cuts meeting in the midline just behind and below the cervix uteri. The inner edge of the peritoneal incision is next brushed inwards all round, so that the pouch of Douglas is collapsed on to the rectum. The rectum is now mobilized on its posterior and anterior aspects, and the lateral ligaments are defined and divided on either side exactly as in the abdominal phase of an abdomino-perineal excision, except that the inferior mesenteric vessels are not divided. However, in male patients it is important to try to avoid the presacral nerve, injury to which would render the patient sterile, and in both sexes to keep close to the rectum when taking the lateral ligaments, in order to avoid damage to the parasympathetic nerves which might impair bladder function or produce impotence.

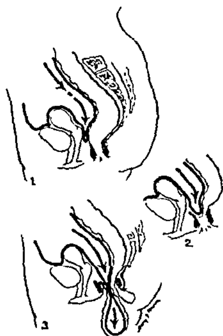


FIG. 20.—Diagrammatic sagittal sections of the pelvis to demonstrate the anatomy of complete rectal prolapse conceived as a sliding hernia of the pouch of Douglas (By courtesy of the Editor of *The British Journal of Surgery.*)

The next step is to draw the rectum strongly upwards out of the pelvis while the puborectalis sling is defined more clearly by scissor dissection on the posterior and lateral aspect of the bowel The rectum is then pushed backwards with the hand while sutures are placed between the two puborectales in the interval between the vagina and rectum. Probably a non-absorbable material such as braided nylon is best for these stitches, and they are most conveniently inserted by means of a boomerang needle. Usually 4 or 5 sutures are employed, the hindermost 1 or 2 enter the muscles on the lateral side of the rectum, so that when they are tied the bowel is apparently somewhat constricted (Fig. 21). If the puborectalis muscles do not come easily together the sutures are tied loosely, but this is seldom necessary. Finally, the redundant rectum is allowed to fall down into the pelvis, while the fringe of pelvic peritoneum on the back of the uterus and around the brim of the pelvis is sutured to the front and sides of the upper part of the rectum and the mesorectum (Fig. 22) In this way the old pouch of Douglas comes to lie below the

new pelvic peritoneal floor. A variant of the suture technique is to insert the stitches in the pubo-rectales behind the rectum, thus pushing the ano-rectal junction forwards. This is technically slightly more difficult but seems to give satisfactory repairs.

There have been no operative deaths or serious complications in 35 cases treated by the author in this way despite the fact that many of the patients were

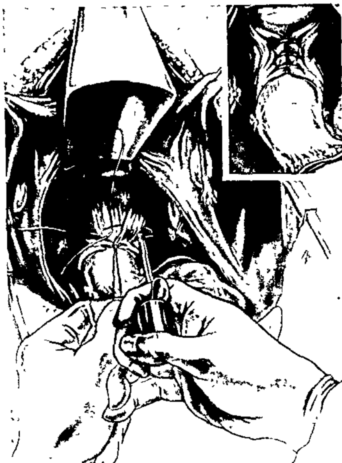


FIG 21.—First suture tied and tails of the knot being drawn taut, causing the puborectales to stand out as two prominent bars of muscle. This facilitates the insertion of the remaining sutures. Inset the complete repair. (By courtesy of the Editor of *The British Journal of Surgery.*)

frail and elderly. A careful follow-up study has disclosed no recurrence of the prolapse, and 14 of the cases have now been followed up for over 4 years.

It would seem that the curative effect of the operation is due in large measure to the adhesions that form around the rectum after its mobilization, though the suture of the pelvic floor and the elimination of the pelvic peritoneal pouch may be valuable additional factors during the immediate post-operative period until the rectum becomes fixed in its bed.

Rectal function after operations for complete prolapse

The prospects of lastin
operations appear excell ... a decided improvement
on recto-sigmoidectomy. ... post-operative rectal function, however, the
results are little, if any, better than those of the latter operation. After the Roscoe
Graham operation only half the patients are fully continent; about a quarter are

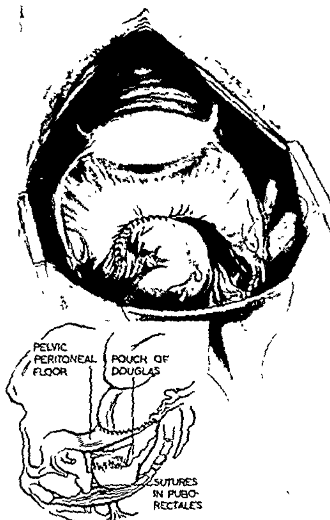


FIG. 22.—Suture of pelvic peritoneum to rectum and mesorectum completed. Inset. diagrammatic representation of relation of new pelvic peritoneal floor to old remnant of pouch of Douglas, and to the puborectalis repair. (*By courtesy of the Editor of The British Journal of Surgery*)

troubled with frequent small motions and impaired control during diarrhoea;
and another quarter are frankly incontinent
constantly. The
so thoroughly w ... leave a great deal to be

desired in some instances. The relative or complete incontinence experienced in these patients is not attributable to the operation but is merely a continuation of a pre-operative deficiency of control This state of affairs in turn is due to the lax atonic condition of the anal sphincters, which is such a notable feature in patients with rectal prolapse, and possibly also to some blunting of normal rectal sensation in these cases (Goligher 1958b, 1959a). Unfortunately it does not seem possible to do anything to improve these imperfections of function and they are likely always to mar somewhat the good results of any operation for this condition.

Palliative treatment of complete prolapse by Thiersch operation

Though anterior resection or the Roscoe Graham operation are well borne even by elderly unfit patients, in any large series of cases of prolapse of the rectum there will always be a few patients deemed unfit for a major intervention of this kind. For such patients the Thiersch operation of circumanal wiring described by Gabriel (1948) is sometimes a useful palliative procedure. Unfortunately if the prolapse is large it is usually only a matter of time before the wire cuts out and infection occurs. But once the sepsis has subsided, a further wire can be introduced, and this performance can be repeated several times. The best results with the Thiersch operation are obtained in small complete prolapses or cases with mucosal prolapse alone. With larger complete prolapses every effort should be made to carry out an abdominal repair or anterior resection if at all possible.

RADICAL SURGICAL TREATMENT OF CARCINOMA OF THE RECTUM

Combined excision

Choice of technique

For most cases of carcinoma of the rectum the standard operation is still a combined excision But of the three main techniques available—the perineo-abdominal, the abdomino-perineal (Miles) and the synchronous combined—the first has never really been accepted, and the second has lost ground steadily during the past decade to the synchronous method, which is now unquestionably the operation most commonly performed for this disease in Britain and the Commonwealth. In America and the Continent of Europe the synchronous technique has not so far achieved much popularity

Extended combined excision

Efforts have been made in the last few years to render the standard combined excision more radical by extending it in an *upward* direction by higher ligation of the inferior mesenteric vessels, in a *lateral* direction by dissection of the lymph glands on the side walls of the pelvis, and in a *forward* direction by multivisceral resections

High ligation of the inferior mesenteric vessels.—The practice of tying the inferior mesenteric artery at its origin from the abdominal aorta instead of at the level of the aortic bifurcation as recommended by Miles (1926) has been prompted by a

desire to deal more effectively with the important upper zone of lymphatic extension along the lymphatics of the superior vascular pedicle. A high ligation of this kind inevitably sacrifices the left colic and accessory or ascending left colic arteries and leaves the descending and sigmoid colon to be nourished solely by the descending branch of the middle colic artery through the marginal artery (Fig. 23*a* and *b*). Some fears might be entertained regarding the adequacy of this supply but observations by Ault, Castro and Smith (1952), Grinnell and Hiatt (1952), Goligher (1954) and Griffiths (1956) indicate that in the great majority of cases the middle colic and marginal vessels are well able to supply the entire left colon down to an iliac colostomy. Gland dissections on operative specimens obtained by radical excision with so-called "flush" ties of the inferior mesenteric artery have been carried out by Grinnell and Hiatt (1952) and McElwain, Bacon and Trimpi (1954). They found that in a few cases metastases were present in glands situated on the

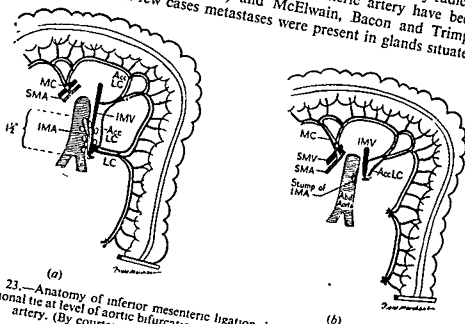


Fig. 23.—Anatomy of inferior mesenteric ligation during rectal excision: (*a*) conventional tie at level of aortic bifurcation, (*b*) high tie at origin of inferior mesenteric artery. (By courtesy of the Editor of *The British Journal of Surgery*.)

uppermost inch or so of the main pedicle, above the origin of the left colic branch. Without a high ligation these glands would certainly not have been removed and the operation would undoubtedly have failed. But with glandular spread as extensive as that it will probably fail anyway even if these glands are removed. It remains to be established by the 5-year follow-up that excision with high ligation has in fact increased the curability rate of radical operation. At the present time the author would not advise that any attempt should be made to secure a high ligation if this involved additional immediate risk as in obese and difficult patients but when it can be easily practised it seems an innocuous procedure which may be of some value and is therefore probably worth doing.

Pelvic adenectomy.—Deddish (1950) and Sauer and Bacon (1952) have sought to enlarge the scope of radical excision by dissection of the internal iliac glands. Bacon and Sauer have practised removal of these glands in addition to radical

excision of growths of the rectum and rectosigmoid in 32 patients. In 11 of these, in whom the growth lay above the peritoneal reflection, no metastases were found in the internal iliac glands, but in 6 of the remaining 21 with extraperitoneal growths, metastases were noted in these nodes. Their experience has therefore demonstrated in a most convincing manner that lateral lymphatic spread does occur with low lying growths—a point on which there has been considerable controversy —but it is debatable whether the attempt at internal iliac adenectomy has accomplished any good. In the author's experience such pelvic side-wall dissections are invariably incomplete and unsatisfactory and often lead to a good deal of bleeding which prolongs the operation considerably. It appears that in the long run they would be associated with a higher operative mortality; they are certainly followed by a greater incidence of post-operative urinary and other complications (Deddish, 1952) For these reasons pelvic adenectomy has not secured an established place in the practice of most rectal surgeons.

Multivisceral resections.—The well-known tendency of cancer of the rectum to become adherent to adjacent organs often presents the surgeon with a formidable fixed mass implicating several viscera. Sometimes the adhesions are purely inflammatory and do not indicate actual malignant invasion (Goligher, 1941) but usually it is impossible to decide on this point at operation and dangerous to attempt to do so because of the risk of spreading growth by separating adherent organs The safer course as a rule is a wide excision removing in part or *in toto* the other viscera involved. It is important to emphasize that such extended excisions are not merely palliative but may on occasions achieve actual cure. This is borne out by a report from van Prohaska, Govostis and Wasick (1953) of Chicago on their experiences with 21 apparently inoperable carcinomas of the rectum or colon for which excisions involving multiple visceral resections were undertaken. Six of these patients are alive and well 5 years after operation and these include 3 who were subjected to hysterectomy along with abdomino-perineal excision Several of the patients had excellent palliative results for 3 or 4 years before succumbing to recurrence. The present author has also had several 5-year cures following excision of the rectum combined with a Wertheim's hysterectomy for rectal carcinoma with proven infiltration of the uterus

In women the problem of the adherent rectal [illegible]
than in men, for [illegible]
relatively simple [illegible]
fixation in front is usually to the prostate, seminal vesicles or bladder and it may be difficult to decide whether to attempt excision and achieve at most only limited removal of these organs or to proceed to the much more radical but extremely formidable step of a complete pelvic clearance. It is particularly galling if, after the latter operation has been done, pathological examination shows that the growth was, in fact, confined to the rectum and that the adhesions were composed of purely inflammatory tissue The author's policy has been to avoid [illegible]
in favou[illegible]
has carr[illegible]
and there have been no 5-year survivors. When complete pelvic clearance is performed it is probably best to implant the ureters into an isolated short loop of

lower ileum draining to the surface as a urinary ileostomy as recommended by Bricker (1950); this avoids the infective urinary complications and electrolyte disturbances associated with colonic or caecal implantation.

Colostomy technique

Immediate mucocutaneous suture.—Until a few years ago most surgeons in making a terminal iliac colostomy simply brought the colon stump through a stab incision in the abdominal wall and left it projecting 2 or 3 inches to guard against retraction owing to abdominal distension or necrosis of the terminal part of the bowel. Subsequent trimming of the colostomy was often necessary 10–14 days later when the colon had become firmly fixed in position. The disadvantage of this technique was that it allowed granulation tissue to form on the peritoneal surface of the projecting bowel; this in due course became converted to fibrous tissue which contracted, often leading to a considerable fibrous stricture at skin level. To avoid this complication Butler (1952) and Patey (1951) have introduced the technique of immediate suture of the end of the colon to the abdominal skin. In the vast majority of cases this is followed by healing per primam without sepsis or mishap due to sloughing or retraction and gives a soft supple colostomy which shows no tendency to stenosis. The present writer has used this method in over 250 cases with generally satisfactory results and can recommend it strongly. Unfortunately the technique is not readily applicable to loop colostomies—as for example a defunctioning transverse colostomy proximal to an anastomosis—if an effective spur is to be provided.

Avoidance of paracolostomy obstructions—The danger of strangulation of a loop of small bowel in the paracolostomy gutter on the outer side of a left iliac colostomy has been emphasized by Gabriel (1928), Goligher, Lloyd-Davies and Robertson (1951) and Rankin (1927), and most surgeons now make a point of closing this space at the time of operation to avoid this hazard. This is best done by means of a purse string suture of linen thread or cotton inserted through the main laparotomy wound before drawing the colon stump to the surface through the separate left iliac stab wound.

An alternative way of obviating the risk of lateral space obstruction in connexion with colostomies (or ileostomies) is to use an extraperitoneal technique as described by Goligher (1958*c*) and Sames (1958) In this method the colon (or ileum) is taken forward to the anterior abdominal wall, not through the peritoneal cavity but in the extraperitoneal tissues round its lateral edge The effect is that no lateral space is created to be closed.

Sphincter-saving resections

In the previous sections of *British Surgical Practice* dealing with carcinoma of the rectum (Lloyd-Davies and Morgan, 1950, Muir, 1952) the position accorded to sphincter-saving resections in radical treatment had of necessity to be tentative. Though the immediate results were known to be satisfactory after certain operations of this type, notably anterior resection, some disturbing local recurrences had been encountered and no long-term follow up was then available. However, this experimental period has been brought to an end by the publication during the

last 2 or 3 years of the 5-year results in large collective series of cases treated by sphincter-saving resections at the Mayo Clinic and St Mark's Hospital (Mayo and Fly, 1956; Morgan, 1955; Waugh, Block and Gage, 1955). It is clear from these comprehensive statistics that for carcinomas of the recto-sigmoid and upper third or even half of the rectum, sphincter-saving resections can offer as good a chance of lasting cure as does a formal combined excision If, however, these operations are to give good results it is essential that they should be adequately performed and reserved for suitably selected cases. In view of the increasing trend of surgical opinion towards these forms of excision, some comments on their scope and the indications for their use may be appropriate.

The extent of tissue removed in a modern sphincter-saving resection

Fig. 24 (*a* and *b*) represents in diagrammatic form the amount of tissue removed in a combined abdomino-perineal excision and an anterior resection respectively.

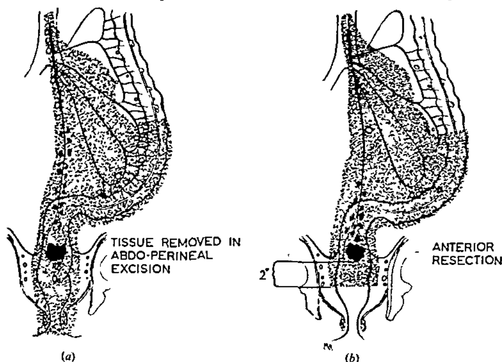


FIG 24 —Diagrams showing the amount of tissue removed in an abdomino-perineal excision and anterior resection respectively, the tissues excised being shown by stippling. (By courtesy of the Editor of *The Practitioner*)

So far as the *upper limit* of the excision is concerned there is no difference at all in the two operations. If the surgeon fancies high ties of the inferior mesenteric artery [illegible] :uvre [illegible] may [illegible]

As for the *lower limit* of the resection, it was originally believed by Westhues (1934) and others that a 1-inch (2·5-centimetre) margin of apparently normal rectal

wall and perirectal tissues distal to the lower edge of the growth would suffice to deal with any retrograde spread in the bowel wall or extramural lymphatics, but more recent work by Goligher, Dukes and Bussey (1951), *Grinnell* (1954) and Quer, Dahlin and Mayo (1953) shows that a 2-inch (5-centimetre) margin is, in fact, desirable.

Laterally, the extent of the two operations is identical. Actually, Westhues (1934) considered that spread along the middle haemorrhoidal vessels was rare and unimportant, but this opinion was based on examination of operative specimens alone, and these contain little of the tissues of the zone of lateral lymphatic extension. It is not uncommon with ampullary or infraperitoneal growths to find the internal iliac lymph glands on one or both sides of the pelvis to be hard and enlarged at operation. Unfortunately, although attempts have been made at block dissection of these glands (Deddish, 1950; Sauer and Bacon, 1952) this is not really a practicable or effective procedure. Lateral spread is thus rather inadequately dealt with by any operation for rectal excision, but sphincter-saving resections need be no more inefficient in this respect than a combined excision.

The dangers of metastases arising by implantation in sphincter-saving resections

The risk of implantation of loose malignant cells on the suture line or in other raw areas during resection operations for rectal cancer has been emphasized by Goligher, Dukes and Bussey (1951), Lloyd-Davies (1950) and Morgan (1950). *It is important to realize that exfoliated cancer cells are present in abundance in* the faeces below the level of the growth, and that their number is increased by manipulation of the growth during operation (Cole, Packard and Southwick, 1954). The plan originally suggested by Lloyd-Davies (1950) and employed by Goligher (Goligher, Dukes and Bussey, 1951; Goligher, 1958*c*), Morgan (1955) and many others, of washing out the rectum from below with 1½–2 pints of 1/500 perchloride of mercury during the operation, to remove or destroy any loose malignant cells, has much to commend it. However, it can only be conveniently practised if the patient is placed in the lithotomy-Trendelenburg position, as for a synchronous combined excision, so that the assistant can pass a proctoscope into the anus during the actual operation. Immediately before this irrigation is given, the rectum is clamped across with a crushing clamp 2 inches below the

to deal with any malignant cells that may be present in this part of the bowel.

It is not easy to determine the precise value of these precautions against implantation, but Goligher (1958*d*) has reported that in his first 35 cases treated by anterior resection there were 4 instances of local recurrence, mostly on the suture line, whilst in his last 102 cases, in which perchloride irrigation, as described above, had been practised as a routine, there were only 2 local recurrences. However, other factors, such as more careful selection of cases and the adoption of a more extensive type of resection, may have been partly responsible for these differences.

Indications for sphincter-saving resection

Height of the growth.—This is the most important consideration determining the

suitability of a case for a sphincter-saving type of resection. Obviously with lesions involving the *anal canal or lower third of the rectum*, that is, up to 7 centimetres from the anal verge on sigmoidoscopy, no question of sphincter-conservation arises, and the correct method of radical treatment is an abdomino-perineal excision. With carcinomas of the *rectosigmoid or the intraperitoneal upper third of the rectum*, that is, from 10 to 20 centimetres or more from the anal verge, the operative indications are almost completely reversed. Statistics from the Mayo Clinic and St. Mark's Hospital show that sphincter-saving resection is just as curative as combined excision for growths at these levels. Moreover, for such intraperitoneal lesions the resection can usually be conducted entirely through the abdomen by the so-called low anterior resection of American surgeons, without having to resort to abdomino-sacral or abdomino-anal techniques to complete the anastomosis, which greatly simplifies the technique of operation and post-operative course. Only very rarely now, usually because of a combination of obesity and a narrow pelvis, should it ever be necessary to employ abdomino-perineal excision for growths of the recto-sigmoid or intraperitoneal rectum.

It is in regard to the treatment of growths of the *mid third of the rectum* (7–11 centimetres from the anal verge on sigmoidoscopy) that controversy still exists. At first sight it would seem that if the lower edge of the growth lies at 7 centimetres and the top of the anal canal is at 3–3·5 centimetres it would be impossible to secure a 5-centimetre margin of clearance below the lesion in a resection operation and preserve [illegible]
operation 7 c[illegible]
saving resecti[illegible]
Waugh (Waugh, Block and Gage, 1955), Mayo (Mayo and Fly, 1956) and Black (Black and Botham, 1958) have used such operations for lesions of the middle third of the rectum with apparently as good late results as those of combined excision for carcinomas of this segment. However, it is usually difficult or impossible to perform an adequate anterior resection for middle-third growths, and an abdomino-anal pull-through technique has generally been employed instead. In the original Bacon version of this operation, which is the one favoured by Waugh, the small ano-rectal stump is denuded of its mucocutaneous lining before the colon is drawn through. This facilitates union between the colon and the anal canal, but none the less, retraction of the colon stump sometimes occurs Further, the absence of normal rectal sensation usually results in patients who have had this operation being essentially incontinent. Only 10 per cent of Waugh's cases had normal control, though another 42 per cent were reasonably satisfied. Eight patients treated by the author, using the Bacon operation, were all incontinent, being totally devoid of rectal sensation and having nothing better than perineal colostomies.

The method used by Black preserves the ano-rectal mucosa and apparently gives good functional results, as does the Maunsell-Weir type of operation, which the author has usually favoured, whereby the anal canal is temporarily everted and direct suture effected outside the anus, between the end of the colon and the cut upper edge of the anal canal or rectum Once the anastomosis is completed, the everted bowel is pushed back into the pelvis. This method, like Black's technique, gives much better functional results than does the Bacon operation, but the

author's experience of it and other forms of abdomino-anal resection is that such resections are especially liable to be followed by prolonged complications owing to sloughing of the colon stump, separation of the anastomosis, and sepsis

It is because of their high post-operative morbidity that the author has come to the conclusion that abdomino-anal resections or especially low anterior resections for middle-third growths are not worth doing. Like Morgan (1955) and Muir (1958) and most other British surgeons who have used conservative resections for rectal cancer, he would recommend that their use should be restricted to growths not lower than 10 centimetres from the anal verge, and that they should invariably take the form of anterior resection; for lesions below this level a straightforward abdomino-perineal excision will be found to give the best overall results.

State of the growth—Morgan (1955) and Muir (1958) both advised against anterior resection for advanced lesions, or for growths shown by previous biopsy to be of a high grade of malignancy The Mayo Clinic surgeons, however, have apparently not observed these restrictions, nor has the present writer made any special effort to avoid advanced carcinomas, though he has withheld anteri- resection in cases with very anaplastic growths, in which this operation might followed by a troublesome local recurrence owing to wide spread in the rectal wa

Presence of hepatic metastases.—When deposits are present in the liver and th excision can only be palliative, anterior resection is a particularly attractive opera tion. At one stage the author was prepared to attempt its use, in these circumstances, for growths at a lower level than he would normally accept for anterior resection with a view to cure, but he would no longer advise any attempt to overstretch the indications in this way, for the complication rate in difficult resections of this kind is unduly high.

Results of surgical treatment

One of the most important events in the surgery of rectal carcinoma in the last few years has been the publication in 1958 of the comprehensive collective statistics of St. Mark's Hospital on the results of radical surgical treatment of this disease (Dukes, 1957; Gabriel, 1957, Lloyd-Davies, 1957; Morgan, 1957) Any surgeon who has to deal with rectal carcinoma should certainly study this report at first hand, and will derive much pleasure from browsing over the many accurate data which it provides.

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ABSTRACTS RELATING TO RECTAL SURGERY

Carcinoma of rectum

Anterior resection

Muir (1958) reports on the use of anterior resection *in the treatment of 114 cases of* rectal and recto-sigmoid carcinoma The 5-year survival rate was 65·2 per cent and there were 6 recurrences. It was considered that the risk of recurrence had been reduced by irrigating and cleansing the rectum below the clamp with a solution of perchloride of mercury, 1 in 500. One patient died from massive pulmonary embolism 9 days after the operation When combined excision was performed in a series of 104 cases the survival rate was only 42 3 per cent Muir is of the opinion that anterior resection should be selected for high rectal growths, for early growths and for growths of low malignancy. In elderly patients the operation yields a relatively low mortality. With regard to technique, Sulphathalidine therapy is recommended for pre-operative sterilization of the bowel. A long lower paramedian incision provides good access to the splenic flexure. After mobilization of the iliac and sigmoid colon, the inferior mesenteric artery is ligated

immediately below the left colic artery. The peritoneum is divided and the rectum is freed as for an abdomino-perineal excision. It is advantageous to carry out some form of lateral clearance and to ligate the ovarian vessels. A final decision is made about the type of operation when the levator ani muscles are completely mobilized. A clamp is applied across the rectum at the chosen site and the anterior rectal wall is incised below the clamp. Division of the rectum is completed with scissors after the insertion of holding sutures. A clear margin of 5 centimetres of bowel must be removed below the growth and a sufficient amount of rectal stump must be left in order to ensure proper continence. The sigmoid colon is cut obliquely and anastomosis is effected with the rectal stump. Penicillin-sulphonamide powder is sprayed round the anastomosis, the pelvic peritoneum is united round the sigmoid and the abdomen is closed. Complications of anterior resection include pelvic and urinary infection, fistulae, stricture, incontinence and recurrence of carcinoma at the anastomotic line.

Carcinoma of rectum and rectosigmoid

Survival after anterior resection

MAYO, LABERGE and HARDY (1958) report on the 5-year survival rate after anterior resection for carcinoma of the rectum and recto-sigmoid. In approximately two-thirds of a series of 507 cases the patients were aged 50–69 years. Usually the growth was found at a level situated 6–14 centimetres from the dentate margin. There was a high incidence of lymphatic node metastases among patients with relatively low-sited lesions. After excluding 25 hospital deaths from the analysis the authors found that the 5-year survival rate was 60·1 per cent. The corresponding figures for patients treated by one-stage combined abdomino-perineal resection and two-stage posterior resection were 51·7 and 46, respectively. For the series of patients who were treated by anterior resection the survival rate was higher among women than among men. The rate was relatively low in patients with lymphatic node metastases and with growths which approached the dentate line. No significant decrease in the operative mortality rate was achieved when concomitant proximal colostomy was performed. Mayo and his colleagues conclude that for adequate resection of carcinoma of the recto-sigmoid and upper part of the rectum it is not necessary to remove the rectal sphincter in all cases. The decision as to removal of the sphincter must be based upon the possibility of removing the lesion from above and excising the intestine far enough below the lesion to control the distal spread of the growth. Usually anterior resection is a difficult procedure. In this context it is noteworthy that the operation cannot be performed unless the instruments are 12–14 inches long.

Carcinoma of mid and upper parts of rectum

Abdominoendorectal resection

DISCUSSING the management of growths of the middle and upper part of the rectum, BLACK and BOTHAM (1958) state that when combined abdominoendorectal resection is performed it is possible to preserve the distal 3–4 centimetres of the rectum and to improve faecal control. Features of the surgical technique include the use of a heavy ligature round the rectum below the lesion. By means of this procedure soiling is prevented during the latter part of the operation. The authors prefer to pack the bowel into the pelvis without attempting to form a new pelvic peritoneal diaphragm. The short segment of the rectum is cleansed after dilatation of the sphincter. Gentle traction is exerted upon the wall of the rectum at the site of the ligature, the rectum is inverted and the entire thickness of its wall is incised 3–4 centimetres above the dentate margin. The mobilized bowel is pulled through the ano-rectal canal and the segment of bowel containing the lesion is excised. Union takes place between the serosa of the colon and the cut end of the rectal stump, but the healing process may take several months. In order to speed convalescence the bowel is trimmed after a period of about 2 weeks. Sometimes a stricture develops at the cut end of the colon. This complication is easily treated by dilatation. Sloughing of

Carcinoma of rectum and colon

Implantation recurrence

LEQUESNE and THOMSON (1958) record 3 cases of implantation recurrence of car-

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excision of the rectum was performed Later on, an adenocarcinoma developed in the perineal region The recurrence was ascribed to implantation of viable tumour cells after accidental opening of the rectum during the operation. Evidence of the continual shedding of viable cells is provided by many authenticated cases of implantation of carcinoma of the bowel in the track of a fistula-in-ano. It is pointed out that manipulation of the growth during the course of an operation may disseminate malignant cells up and down the bowel As far as possible the desquamated cells must be prevented from coming into contact with a raw area. For example, if sigmoidoscopy reveals the presence of benign adenomas situated distal to a carcinoma it is advisable to excise the proximal tumour before operating on the distal growths Prophylactic measures include the use of a solution of perchloride of mercury as an irrigating agent. Before excising the carcinomatous tissue, Cole ties tapes round the bowel immediately above and below the growth. This procedure is of assistance in preventing the spread of the desquamated cells

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THE PROBLEM OF RECURRENCE AND MALIGNANCY IN TUMOURS OF THE PAROTID

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Although constituting only a small percentage of all tumours, parotid tumours have always excited an interest out of proportion to their frequency. In the early days of the modern era, the interest was in the variations of their microscopic morphology and in speculation on their origin Later, interest shifted to their variability of behaviour, and in particular to the problem of recurrence after apparently successful removal of tumours commonly regarded as benign

The classification of a tumour as benign or malignant is more difficult in the parotid than in many other organs. A typical benign tumour grows by expansion, displacing the surrounding structures, whereas a malignant tumour grows by infiltration and also may metastasize. The difficulty with the parotid is that, although distinct histological types of tumour are distinguishable, in many of the named types all shades of behaviour are represented varying from circumscribed, well-differentiated, slow-growing tumours to tumours which infiltrate and metastasize early. The most malignant and least differentiated members of each group thus merge into the carcinoma group Even the essentially expansile mixed tumours, which constitute approximately 75 per cent of all tumours of the parotid, sometimes have microscopic foci of infiltration which account in part for their tendency to recur after enucleation. Such recurrences are sometimes macroscopically infiltrating and may kill by local spread.

In this article, recurrent mixed tumours are discussed first. Adenolymphoma is not discussed here, although this expansile encapsulated tumour of the parotid may show apparent recurrence after operation. This phenomenon is not an example of true recurrence, but of multiple primary tumours (Patey and Thackray, 1958); moreover, recurrent adenolymphoma does not kill. The tumours other

than recurrent mixed tumours which are discussed—cylindroma, muco-epidermoid tumour, and carcinoma—are all non-encapsulated, infiltrating, and in varying degree metastasizing.

The present position of parotid surgery

Before discussing recurrent and malignant parotid tumours, a brief reference to the present position of parotid surgery may help to put the subject in proper [illegible]

nerve is preserved, any facial paralysis will be only temporary. A further important practical consideration is that an accurate clinical diagnosis of the nature of a parotid tumour is usually impossible. The operation is thus primarily exploratory, the precise therapeutic procedure depending upon the result of the exploration.

Material

In the 7 years from the beginning of January, 1952, to the end of December, 1958, the present authors operated on 114 parotid tumours, of which 42 were recurrent or malignant. They are subdivided as shown in the Table.

TABLE

Number of Recurrent or Malignant Parotid Tumours Submitted to Surgery, January, 1952, to December, 1958

	Cases
Recurrent mixed tumour	18
Cylindroma	3
Muco-epidermoid tumour	6
Carcinoma	14
Lymphoblastic sarcoma	1
Total	42

RECURRENT MIXED TUMOURS

Incidence

The incidence of recurrence of mixed tumours following operation is difficult to determine owing to the unconscious selection in most reported series. Figures can be found of recurrence rates varying from less than 5 per cent to as high as 50 per cent. The factor of the length of follow-up is also important, the incidence of recurrence increasing progressively with time (Kirklin and his colleagues, 1951).

One cause of a fallaciously low recurrence rate is a tendency to transfer cases that have done badly to separate semi-malignant or malignant groups, thus improving the prognosis of the remainder. On the other hand, many writers report a fallaciously high incidence of recurrence through regarding the proportion of

recurrences to primary tumours treated as the recurrence rate. This would be justifiable if applied to all cases operated on, and if the figure could be determined. There is, however, a natural tendency for surgeons to refer recurrences of mixed tumours to tumour centres, which thus deal with an unduly high proportion of recurrences. In the present series, there were 18 cases of recurrent mixed tumour of the parotid during a period in which we operated on 50 primary mixed tumours. A similar proportion of operations for recurrences to operations for primary mixed tumour is common to many centres. Though the absolute incidence of recurrence is, as in our series, usually impossible to determine, there is general agreement that recurrence is too frequent to be accepted with equanimity. The modern more active surgical treatment of parotid tumours results largely from this dissatisfaction with the past results of the treatment of mixed tumours.

Clinical features of recurrent mixed tumours

In most cases, the only feature is the symptomless reappearance of a lump or lumps in the operation area. Usually the lumps are smooth and well demarcated like the primary tumour; occasionally, they are irregular and infiltrating. Infiltration of the skin is usually obvious clinically, but infiltration of the masseter, and less commonly of the periosteum of the zygoma, the temporal fascia and the ligaments of the temporo-mandibular joint may be found at operation though not detected clinically.

Of the 18 recurrent mixed parotid tumour cases of our series 9 had had one operation before coming under our care, 6 two operations, 2 three operations, and 1 four, making a total of 31 operations. The 2 cases that had had 3 operations had also each had another operation for the insertion of radium needles, and if these are added the total operations rise to 33. We performed 19 operations on these 18 cases, the extra operation resulting from our not realizing in an early case the necessity of excising the whole of the original operation scar, and to the development of a further nodule in the unexcised portion of the scar. Adding our 19 operations, a total of 52 operations has been performed to date in the attempt to rid these 18 patients of their disease, and the end has not necessarily been reached.

One patient is known to have had radium needles inserted into the tumour bed at the primary operation; 2 others, as already noted, had radium needles inserted into recurrences; several others had various other types of irradiation either following the primary operation or for the recurrent disease, without obvious benefit.

Pathology of recurrent mixed tumour

We have dealt at length elsewhere (Patey and Thackray, 1958) with the features of mixed tumours which explain their liability to recur after enucleation. Briefly, these are the presence of multiple microscopic focal infiltrations through the peripheral condensation of fibrous tissue; subcapsular splitting so that a thin layer of tumour tissue is left behind; and thirdly, a nodular surface, some of the projections having such a narrow stalk that they may be broken off and left behind. This last feature is also of significance in that such projections, if their stalk of attachment is not in the plane of section, may appear in microscopic preparations as separate nodules. Such nodules are often said to be "satellite nodules" and to

indicate multi-focal origin, but in our serial section study primary mixed tumours were always solitary. By contrast, recurrences are often made up of a large number of secondary nodules (Fig. 25) which by serial sectioning can be shown to be in the field of the original operation (Ackerman and Wheat, 1955) Apart from recurrences developing from tumour cells left behind at the periphery, cells may be implanted into the wound by rupture of soft tumours. Such recurrences are often found in the line of the skin incision, which should therefore always be excised (Fig. 26).

In addition to their multiplicity, recurrent mixed tumours are more likely than primary tumours to infiltrate, and may after many years metastasize. There may be an accompanying histological change, the tumour becoming less well differentiated, but in one patient, not in this series, we have seen distant metastases

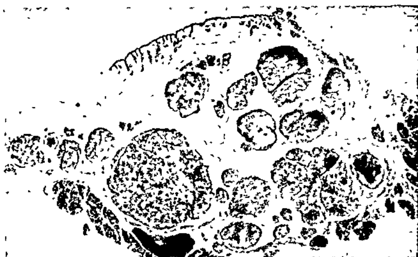


FIG 25.—Recurrent mixed tumour Parotidectomy specimen cut across showing skin with old scar above, normal parotid lobules on extreme right and bottom left, with large numbers of discrete tumour nodules present (×3).

indistinguishable histologically from a typical mixed tumour occurring 20 years after the primary operation.

Treatment of recurrent mixed tumours

The treatment of all the types of tumour under consideration is discussed later. Here we will consider only the main lines of treatment in the recurrent mixed tumour group. In 15 of our 18 cases, it was possible to perform a parotidectomy with complete preservation of the facial nerve except for the occasional sacrifice of one or two small branches involved in tumour. In 2 cases parotidectomy with complete sacrifice of the facial nerve was performed, and in 1 case parotidectomy with sacrifice of the main upper division of the nerve which had already been partially divided at a previous operation. Apart from the one case already noted, the scars of previous operations were always completely excised.

Because of the usual multiplicity of nodules in recurrent mixed tumours, conservative parotidectomy is not as sound a procedure pathologically as it is for primary mixed tumours. An expression of this is that Redon and Belcour (1955) had four recurrences after 62 parotidectomies for recurrent mixed tumour while they had only one recurrence following 127 parotidectomies for primary mixed tumour. Preservation of the facial nerve is, however, so important cosmetically that a minor compromise with pathological soundness may be justified. On the other hand, if the facial nerve or one of its branches is infiltrated or surrounded by tumour, the time for compromise has clearly passed.

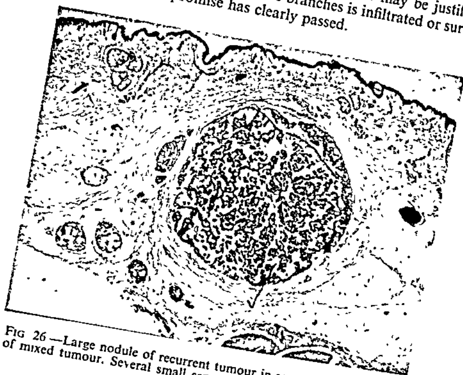


FIG 26—Large nodule of recurrent tumour in scar following removal of mixed tumour. Several small separate nodules can be seen nearby (×13)

Results

Apart from the one case in which the patient developed a further nodule in the portion of scar not excised at our original operation, no patient has to date developed a further recurrence. It is in most cases too soon since the operation for this to be of significance, and a detailed analysis of results will not be given

Illustrative case history—case 1

Recurrent mixed tumour

A man, aged 59 years, presented in September, 1958. He was first treated for a tumour of the right parotid in 1951, when a mixed tumour was removed by enucleation. There was an early recurrence which was again removed locally in 1952. A further recurrence in 1953 was treated by the insertion of radium needles. In 1956, a superficial conservative parotidectomy was performed. A further recurrence was re-explored in May, 1958, and tissue removed for histological examination which showed persistence of the mixed tumour.

CYLINDROMA

This is an epithelial tumour with a characteristic histological appearance (Fig 27), which may occur in the major salivary glands but more commonly in the minor salivary glands and in the mucous glands through the respiratory tract

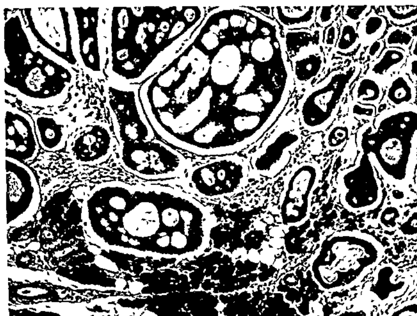


FIG 27.—Typical cylindroma. Notice lack of demarcation between tumour and normal parotid tissue below (×95).

(Ranger, Lucas and Thackray, 1956) Though occasionally remaining circumscribed for a time the tumour tends to infiltrate slowly but inexorably, often along nerves, and there may be a history of the excision of repeated recurrences over a course of 10 years or more before the tumour kills by direct spread, sometimes associated with terminal metastases. In other cases, the tumour may change its histological type and disseminate as an undifferentiated carcinoma; in these, the origin of the carcinoma in a previous cylindroma may only be realized if there have been previous biopsies or by the demonstration of cylindromatous areas in carcinomas Cylindromas constitute only a small proportion of all parotid tumours. There were three examples in our series. One was that of a man, aged 45 years,

who presented with a primary tumour which had been present for 20 years, and which had recently grown more rapidly and become painful The second case was that of a woman, aged 61 years, who had also had a parotid tumour for 20 years with recent increase in size and pain. The history of the third case is given in more detail below. In no case was the diagnosis made before operation.

Treatment

In the two cases of primary cylindroma, it was possible to preserve the facial nerve except for one or two small branches found at operation to be involved in growth. In the recurrent case, it was possible to preserve the facial nerve in spite of the necessity to remove most of the masseter because of its infiltration by growth. Cylindroma is sensitive to irradiation, and routine irradiation is a rational adjuvant to surgery. Post-operative irradiation was given in all three cases.

Illustrative case history—case 2

Recurrent cylindroma infiltrating the masseter

A married woman, aged 31 years, attended another hospital in 1955 for a tumour in the left parotid gland of 6 months duration. Local removal was carried out, but the tumour recurred 6 months later. We re-operated in April, 1957, and found a tumour in the subfacial parotid which had extensively infiltrated both the gland and the underlying masseter, but which had not involved the facial nerve. Total parotidectomy was performed together with removal of the old scar and of most of the masseter, the facial nerve being preserved There was slight post-operative facial weakness which rapidly recovered Post-operative irradiation was given to the left parotid region to a total dose of 5,432 rads. The patient remains well to date. Pathological examination showed a typical cylindroma infiltrating the parotid gland, the masseter, and the adjacent fibro-fatty tissue.

MUCO-EPIDERMOID TUMOURS

These growths are characterized histologically by a mixture of squamous epithelium and columnar mucus-secreting epithelium in varying proportions. Originally described as being either benign or malignant (Stewart, Foote and Becker, 1945) they are regarded by more recent writers as being all malignant to a varying degree. The better differentiated examples often contain mucus-filled cysts which may rupture during operative removal, releasing mucus and papillary fragments of growth which may become implanted in the wound. In the more malignant varieties there is less production of mucus, but the growths metastasize to the regional glands at an earlier stage (Fig. 28).

Clinically, muco-epidermoid tumours have no diagnostic features but present like most other parotid tumours as symptomless lumps. Pathologically, they constitute a more heterogeneous group than those already discussed. Our 6 cases can be divided macroscopically into three pathological groups:

(1) In 2 cases, the tumours constituted slow-growing, well demarcated but non-encapsulated, multicystic, solitary nodules.
(2) In 2 cases, the tumours were infiltrating the parotid gland, and in 1 case the masseter also, but there was no lymph node involvement.
(3) In 2 cases, one of which was a recurrent case, there was lymph node involvement in addition to local infiltration.

Treatment and results

All cases were treated by conservative parotidectomy. Formal lymph node dissections were not carried out and the two examples of microscopic invasion of the lymph nodes were discovered on routine examination of upper deep cervical lymph nodes removed locally at the primary operation All patients are alive and well at periods varying from 6 months to 5½ years after operation, including both cases with lymph node involvement. The history of one of these cases is given below and also the history of the case with invasion of the masseter. We have no information on the radio-sensitivity of muco-epidermoid tumours, but we have, in fact, treated the 4 cases in which infiltration was present by post-operative irradiation.



FIG. 28 —Invasion by muco-epidermoid tumour of upper cervical lymph node in which there are small cysts full of mucus (×80)

Illustrative case histories—cases 3 and 4

Muco-epidermoid tumour invading masseter

A married woman, aged 39 years, presented in June, 1953, with a lump 1¼ inches in diameter in the left parotid which had been slo...

sligh...
was...
sho...
The patient remains well to date.

Muco-epidermoid tumour with lymph node involvement and secondary invasion of sternomastoid

A boy, aged 16 years, presented in June, 1953, with a lump in the right parotid region of 1 year's duration. At operation, an infiltrating mass was found in the lower part of the [illegible]

[illegible] upper deep cervical region (Fig. 37). In June, 1955, a further mass developed infiltrating [illegible]

[illegible] lip which has persisted since the second operation.

CARCINOMA

Mode of clinical presentation

The 14 cases of carcinoma, like the muco-epidermoid tumours, also presented in heterogeneous fashion in five different ways:

(1) Four cases presented as symptomless tumours of the parotid indistinguishable clinically from other parotid tumours Three cases were treated by conservative parotidectomy, and the diagnosis of carcinoma was not made until subsequent pathological examination. Two of these patients are alive and well at 2½ and 3½ years; the third whose history is given below died from generalization of the disease after early local and lymph node recurrence in spite of treatment by radical local and glandular dissection. In the fourth case, the trunk of the facial nerve was found to be involved in growth and had to be sacrificed. This patient is alive and well 1½ years after operation

(2) Two patients presented with facial paralysis In one the tumour was so inconspicuous that it was not noticed by the patient. The cause of this unusually early facial paralysis was that the tumour had originated in the region of the stylomastoid foramen into which it had extended. This patient was treated by radical parotidectomy with sacrifice of the facial nerve, and she is well 1 year later. The other patient with facial paralysis had an irregular infiltrating tumour of some months' duration. She was treated by radical parotidectomy and is well, but the operation was only a few months ago.

(3) In 5 cases, the carcinoma developed from inert and apparently benign tumours, which in 4 cases had been present as primary tumours for many years. The tumours had recently grown more rapidly; in 2 cases there was clinical evidence of local infiltration though not involving the facial nerve; and in 1 a hard lymph node had developed in the upper deep cervical chain. In the fifth case the carcinoma developed in a recurrent mixed tumour. A man, aged 58 years, had an operation for mixed tumour in 1939. A recurrent nodule appeared very quickly but remained inert for 19 years, when it began to grow quickly and to show infiltration of the skin and fixation to deep structures associated with early facial paralysis (Fig. 29).

Three of the 5 patients were treated by radical parotidectomy with complete sacrifice of the facial nerve, one in addition having a radical lymph node dissection. The remaining 2 had partial sacrifice of the facial nerve, one main branch being

uninvolved and preserved. One patient has died of his disease; this was the patient who had a clinically invaded cervical lymph node and on whom a block dissection was performed. Two are alive and well at 1–2 years; the remaining 2 are well but were operated on only last year.

(4) Two cases presented originally to other hospitals with lumps which were clinically indistinguishable from simple tumours and which were treated by local removal, in one case followed by x-rays. When we first saw the patients, the diagnosis of carcinoma had been established microscopically and both tumours had recurred locally. One was a woman, aged 50 years, and the other a girl, aged 11 years Both cases were treated by wide removal of the growth, the overlying skin, and underlying structures including the masseter. Both soon developed further recurrence in the operation area and one, the girl, died within a short time from generalization of the disease.

(5) The final method of presentation was as a rapidly developing lump in the parotid region which occurred in a man, aged 52 years, whose history is given



FIG. 29.—Pre-operative photograph of patient with carcinoma of the left parotid which developed from a recurrent mixed tumour of 19 years' duration. The paralysis of the left orbicularis oris is shown.

below (case 6). The picture was reminiscent of the acute inflammatory carcinomas of the breast met with during lactation.

Illustrative case histories—cases 5 and 6

Carcinoma recurring and metastasizing after multiple operations

A man, aged 33 years, presented in July, 1953, with a lump 2 × 1 inch in the left parotid region of 1 year's duration He was at first told it was a "cyst" and advised to ignore it. After about 4 months it started to increase in size more rapidly and to become painful. As a result he sought further advice. In August, 1953, operation was performed and a tumour found in the suprafacial parotid. The facial nerve was not [illegible]

[illegible]

of 5,400 rads

In January, 1954, he began to complain of pain in front of the left ear, and subsequently

the lower part of the cartilaginous external auditory meatus became thickened. He was readmitted and on January 22 a block removal of the remains of the left parotid was performed together with the facial nerve, the whole of the cartilaginous external auditory meatus, the lower part of the pinna, part of the masseter and part of the posterior belly of the digastric. Pathological examination showed an infiltrating nodule of carcinoma, removal of which appeared complete. It was noted, however, that the growth had invaded lymphatics and venules. On February 9 a block dissection of the left side of the neck was performed. Pathological examination showed invasion of two glands by carcinoma. In May, 1954, further nodules appeared in the operation area, and later intracerebral and pulmonary metastases developed. The patient died in July, 1954.

Acute inflammatory carcinoma

A man, aged 52 years, presented in May, 1958, with a history that 2 months previously [illegible] Histological [illegible] to a [illegible] on, in [illegible] cided [illegible] igger, [illegible]

Pathology of carcinoma

The tumours in this group of 14 cases were as varied pathologically as in their mode of clinical presentation, and are grouped together only by the common factors of poor differentiation and rapid infiltrative growth (Fig. 30) The fact that we have a separate group designated carcinoma does not imply that the tumours previously dealt with are not malignant.



FIG. 30 —Carcinoma of parotid Halved operation specimen showing parotid to the right of the tumour mass, infiltrated muscle to the left and skin above.

In the 5 cases in which the tumour had developed from long present inert growths, section of the operation specimen revealed a circumscribed lesion (Fig. 31) with nondescript white tumour tissue extending out from it and infiltrating surrounding structures indiscriminately. A similar picture of another of the 5 cases was illustrated in a previous publication (Patey and Thackray, 1958).



FIG 31 —Parotidectomy specimen cut across showing an ovoid tumour of long standing, indicated by arrows, with infiltrating white carcinomatous tissue extending out from it.

Histologically, the central residual tumour was cylindromatous in one case and of mixed tumour type in three; in the fifth case the circumscribed central tumour nodule was partly necrotic and the remainder was overgrown by anaplastic carcinoma. The infiltrating parts of these tumours were so de-differentiated that no more precise histological designation was possible than spindle or spheroidal cell carcinoma, according to the shape of the tumour cells (Fig. 32)

Of the tumours which pursued a malignant course from the start it was possible to find areas suggesting that 3 cases had resulted from de-differentiation in cylindromas, whilst in 3 others the cells were epidermoid (Fig. 33).

The most malignant tumour, the acute carcinoma described in case 6, was only seen in a biopsy specimen. The tumour cells were so anaplastic that the problem of distinguishing them from malignant reticulo-endothelial cells was very great. In one case in the series an anaplastic tumour was diagnosed as a lymphoblastic sarcoma, and there are in the substance of the parotid lymph nodes from which such tumours can arise A further source of difficulty may be the lesion which Godwin (1952) called the benign lympho-epithelial lesion, and which we believe to be inflammatory (Patey and Thackray, 1955), but which may in a small biopsy easily be misinterpreted as neoplastic.

The intraparotid lymph nodes may be early invaded by carcinoma of the parotid, but whether by lymphatic or direct spread may be difficult to determine. Lymph nodes from the cervical chain were available for examination in 8 cases



FIG 32 —Spheroidal cell carcinoma of parotid, with a normal duct also shown (×200).

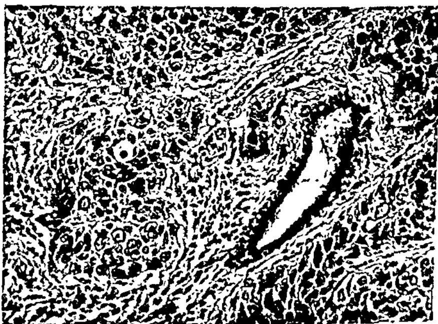


FIG. 33.—A small normal parotid duct surrounded by epidermoid carcinoma (×170).

and were found to be invaded in 3; 2 of these are already dead, the third is recent. Malignant cells were identified in samples of blood removed from the external jugular vein at the time of operation (Fig. 34) in 3 patients; they are alive and well, but the operations were only done within the past 6 months

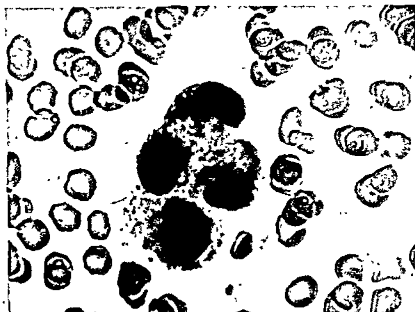


FIG. 34 —A group of carcinoma cells in blood removed from the jugular vein at the time of operation on a patient with carcinoma of the parotid

SOME POINTS IN THE SURGICAL TREATMENT OF RECURRENT AND MALIGNANT PAROTID TUMOURS

Most cases, whether they present as undiagnosed parotid lumps or as recurrent tumours, are explored with the aim of preserving the facial nerve if it is possible to combine such preservation with adequate removal of the growth. Even in infiltrating tumours, such a conservative procedure is often possible (see Fig. 35), but the decision can only be made at operation. All patients undergoing operation for parotid tumours should therefore do so in the knowledge that partial or complete sacrifice of the facial nerve may occasionally be necessary. The decision is usually based on naked eye evidence of involvement of the nerve in growth, but occasionally immediate microscopical examination may be helpful (Fig. 36). If the facial nerve is uninvolved, the standard conservative parotidectomy is performed through the usual cosmetic cervico-facial incision.

If a previous operation has been performed, the scar should be excised in view of the frequency with which deposits of growth are present. The fact that such excision will involve the surgeon in difficulties in the closing of the wound should not influence him If the preliminary exploration reveals that the trunk of the

facial nerve is involved in growth and will have to be *sacrificed, it may be advan*ageous to divide the nerve well behind the level of involvement by chiselling off th mastoid and styloid processes and the termination of the stylomastoid cana Apart from this, removal of the mastoid process is rarely helpful in parotid surgery

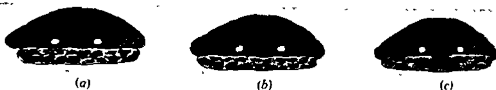


FIG. 35.—Diagrammatic representation of section of parotid gland overlying the [illegible] branches of the facial nerve. The black area repre-

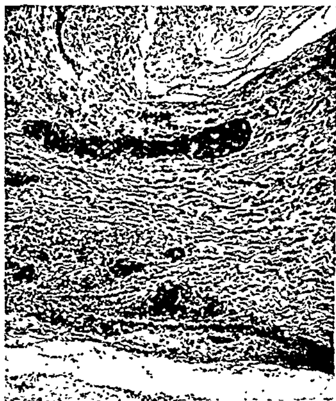


FIG. 36.—Longitudinal sectio of facial nerve a little way fron a carcinoma of the parotid showing growth of tumour cell along the nerve. Frozen sectio at time of operation (×80)

the only exception being when the tumour is so close to the mastoid that separation runs the risk of rupturing the tumour.

The most frequent deep structure to be involved is the masseter, and *its removal* to the required extent presents no difficulty. Often this can be done without sacrifice of the facial nerve or with sacrifice of the intermediate branches only. Removal of the mandible is rarely necessary and was not done in this series Removal of the cartilaginous external auditory meatus was carried out in one case

of recurrent carcinoma (illustrative case 5) but, as in this case, when such removal is necessary the disease is likely to be so advanced and highly malignant that the outlook is poor. We have only done formal block dissections of the neck in cases of carcinoma with clinical evidence of lymph node involvement, though as already noted we remove an upper deep cervical node for diagnostic purposes almost as a routine in parotid tumours. Both cases in which we did a formal block dissection of the neck died of the disease. Clinical lymph node involvement in carcinoma of the parotid is thus of serious prognostic significance.

In most cases, primary skin apposition is possible even when moderate amounts of skin have to be removed. Occasionally a rotation flap from the retroauricular region may be necessary before skin apposition is achieved. In 2 cases we have used a retroauricular pedicle flap with the base inferiorly to cover a particularly large skin deficiency, the donor area being covered by a free skin graft.

In the treatment of permanent facial paralysis we have used two procedures, lateral tarsorrhaphy for the lower eyelid and nylon slings for the lower face. Lateral tarsorrhaphy, which is carried out by our ophthalmological colleagues about a week after the primary operation, is an extremely satisfactory operation, and in our opinion should replace sling operations on the lower lid. The nylon slings to the lower face are inserted like fascial slings. Though in one case at the end of 18 months a nylon sling ulcerated through the overlying mucous membrane and had to be removed, we have found the procedure, in general, simple and satisfactory, at any rate as a temporary measure until a more formal plastic procedure can be done by the plastic surgeon (Fig 37)



FIG 37 —Same patient as Fig 45 after radical parotidectomy with sacrifice of facial nerve. A partial tarsorrhaphy has been performed on the left side, and nylon slings inserted to support the lower face.

THE POSSIBILITY OF IMPROVEMENT IN RESULTS

The application of the standard surgical principles in the treatment of tumours—early operation and wide removal—were late in being applied to the parotid. Many of the unsatisfactory results now seen should disappear with the general adoption of modern surgical techniques Mixed tumours are of such low malignancy that recurrence should theoretically be almost abolished with early operation, wide

removal and avoidance of cell spill. At the other end of the scale, some carcinomas should be preventable by operating in the precarcinomatous inert stage. Our results, though too soon after operation to be conclusive, suggest that some developed carcinomas may also be curable, and also some of the tumours of intermediate malignancy of the cylindroma and muco-epidermoid groups. There will remain, however, as in other regions, a hard core of highly malignant tumours for which present methods of treatment are inadequate and for the cure of which we must await fundamental advances in knowledge.

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ABSTRACTS RELATING TO PAROTID TUMOURS

Diagnosis and management

[illegible] performed for the removal [illegible] ours and 29 patients [illegible] re aged 16–82 years. [illegible] Warthin neoplasms [illegible] and muco-epider-moid tumours affected more women than me[illegible] were more often encountered in men. As for [illegible] procedure of choice. After a Y-shaped incisi[illegible] [illegible] ase was [illegible] was per-[illegible] [illegible] and [illegible] ach [illegible] several [illegible] of wide centimetres towards the hyoid bone. Infiltrating growths were treated by [illegible] excision and neck dissection. Sometimes radiotherapy was also employed. Salivary fistula developed in 6·5 per cent of the cases treated by subtotal parotidectomy. The

tumours.

Pathology and treatment

PATEY and THACKRAY (1958) report on 80 cases in which parotidectomy was per-

advisable. If enucleation is adopted in the management of primary mixed tumours there

planted in the scar of the original incision.

Treatment

PATEY (1958) points out that in 1907 Carwardine recorded a case in which total paro-

grafts for the primary operation.

Recurrent mixed tumours of the major salivary glands

Management

KEIM (1958) reports on the surgical treatment of recurrent mixed tumour affecting the parotid gland (9 cases) and the submaxillary gland (1 case). The series comprised 5 men and 5 women aged 28–65 years. In every case there had been at least one attempt to remove the tumour by blunt dissection, but haemorrhage from the wound had made the procedure difficult and rupture of the tumour had led to dissemination of the cells. Eventually the cells had multiplied to form recurrent nodules. X-ray therapy was employed in the management of 3 cases, but the treatment proved to be ineffective. In the surgical treatment of the recurrent parotid tumours care was taken to isolate the facial nerve near the site of its emergence from the stylomastoid foramen; then the diseased tissue was resected by partial parotidectomy. A Y-shaped incision was made, with the upper limbs of the incision placed respectively in front of and behind the ear. If examination revealed that the nodules had reached the orifice of Wharton's duct the anterior part of the gland was exposed by extending the incision horizontally from the anterior limb of the Y. The gland tissue superficial to the facial nerve was resected with the nodules. When [illegible] tumour was removed by total resection of the gland. In order to obtain access to this tumour it was found necessary to resect the ascending ramus of the mandible. After surgical treatment of the series of cases no evidence of recurrence of the disease was detected during an observation period ranging from 12 months to 10½ years. Six patients were free from the disease for at least 4½ years. Transient post-operative paresis of the lower lip was recorded in 3 cases. Total paralysis of the facial nerve occurred in 2 cases, but the paralysis cleared completely within 2 months of the operation.

Chronic or recurrent sialadenitis

Parotidectomy

KEENAN, BEAHRS and DEVINE (1958) give an account of the use of parotidectomy in the [illegible] was not considered to be of value in selecting patients for operation. Parotidectomy was performed because irreversible changes had taken place in the parotid gland, with obstruction due either to a stone in Stensen's duct (1 case) or to inflammatory swelling (4 cases). [illegible] in 2 cases, but the paresis was transient. In no instance was the facial nerve injured permanently. Superficial parotidectomy was preferred to total parotidectomy. The authors point out that the former operation can be performed with relative ease and with less chance of injuring the facial nerve. With reference to technique, the trunk of the nerve is exposed as it enters the substance of the gland. Under direct vision the glandular tissue situated superficial to the nerve is dissected from the trunk and its branches.

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PROGRESS IN ENDOCRINE SURGERY

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Since the last review of the endocrines two years ago (Taylor, 1957), there has been a general quickening of interest in endemic goitre in many parts of the world and a special number of the *Bulletin of the World Health Organisation* was issued in January of last year (1958) which covered the subject in a most comprehensive manner. Evidence has been coming in from Israel, where there has been an epidemic of de Quervain's subacute thyroiditis, that in this outbreak at least the disease may be due to the mumps virus.

In other fields there have been further attempts to graft endocrine tissue into patients suffering from hypoparathyroidism and these appear to meet with varying partial success.

In the adrenal field more reports of aldosterone secreting tumours have appeared, but the condition seems to be a rare one.

THE THYROID GLAND

Endemic goitre

Volume 18 of the *Bulletin of the World Health Organisation* was devoted to 6 articles covering the subject of endemic goitre and by far the most important of these was the one by Kelly and Snedden (1958) on the prevalence and geographical distribution of goitre This review is a remarkable piece of work covering every country in the world from which data have been received concerning goitre, and giving the most comprehensive series of references which are available at the present time. The authors estimate that the total number of goitrous people in the world today is probably not far short of 200 million, and it would appear that the geographical distribution of the condition has not altered in the last 100 years, although the intensity of the disease has substantially declined. In a few countries where it has done so, it has been *pari passu* with an increase in the standard of living. It is still true that the most notorious goitre centres of the world are located in high mountain regions—in Alpine valleys, in the Pyrenees, on the slopes of the Himalayas and along the Cordillera of the Andes. Goitre may also be encountered,

however, at sea-level and is endemic in parts of Finland and the low-lying Netherlands.

Geochemistry provides a ready explanation for the distribution of goitre. The types of terrain in which the condition is for the most part found, whether at high altitude or low, are those which have been subjected either to flooding or to intense glaciation and from which most of the soil iodine has therefore been washed out and carried down to the sea.

There are still many countries today where the incidence of goitre is exceedingly high and causes a serious drain on the resources of both medical and social services. This is all the more tragic when it is realized that simple goitre is a readily preventable disease, only requiring the addition of a small amount of iodine to table and cooking salt for this to be achieved in most civilized countries (Matovinovic and Ramalingaswami, 1958). In other parts of the world where salt is obtained locally, iodine can be introduced into flour or sweets so as to augment the diet. In New Zealand and Switzerland, where iodized salt has now been in constant use for a considerable time, the endemics have been largely eliminated, but in England and Wales it is estimated that there are still about 500,000 cases of thyroid enlargement in school children and young adults. It is really essential for us all to agitate that table salt in Great Britain be iodized in order to reduce this number.

The thyroid nodule

This subject still continues to attract a considerable amount of attention and the present author has reviewed his own experience (Taylor, 1958), describing the *differential diagnosis, natural history and complications* of simple, toxic and malignant nodules. The evolution of the simple nodule has been shown by autoradiography to consist of focal hyperplasia which involves usually some 50-60 follicles in a functional group and goes on typically to central haemorrhage, necrosis and resolution. The end-result is non-functioning, and other foci of activity then appear elsewhere in the gland. Thus, eventually *a multinodular goitre* is produced in which only a few nodules will be found to be active.

The diagnosis of a solitary nodule in the thyroid is one of some importance, for such an area may occasionally harbour malignant disease; surgical excision therefore is always recommended for solitary nodules in young patients. However, many nodules which appear solitary on clinical examination are shown at operation to be accompanied by many other smaller nodules in the gland. As a result, attempts have been made to evolve methods which might help in the diagnosis of
the malignant nc for
reducing the size
36 patients with
twice daily, raising the dose every few days to a maximum of about 200 microgram
a day The serum cholesterol and the basal metabolic rate were determined frequently and a tracer dose of radioactive iodine was given to the patient and the *neck scanned. They stated that all the goitres* became smaller and in more than half of them the reduction was to less than 50 grammes, which would mean that they were only barely detectable clinically. Only one did not regress as expected and on excision this was found to be a cancer. They also stated that in a patient

who has had the whole of the thyroid removed, 5 grains (300 milligrams) of dried thyroid are required daily to maintain the euthyroid state.

Other uses for T.3 have been reviewed by Goolden and Burrell (1957). The main advantages of T.3 over dried thyroid and thyroxine are that it has a much more rapid action and its effects are transient. It is, of course, more active weight for weight than thyroxine, but there is no evidence so far that its action differs in any way other than a quantitative one from that of thyroxine A patient maintained on T.3 after total thyroidectomy, as in the treatment of thyroid carcinoma, will become myxoedematous within 12–14 days after stopping the drug This will result in saving the patient much time and discomfort when the treatment of thyroid cancer with radio-iodine is planned.

Another [illegible]
pointed ou [illegible]
radioactive [illegible]
a repetition of the test would still show a raised iodine uptake in the toxic patient, but suppression of the uptake in the non-toxic patient. Using T.3 the same test can be carried out in 6 days since the response to the drug is so much quicker.

Finally, when there is a suspicion of hypothyroidism, one of the best diagnostic tests is to give hormone replacement and this is much more quickly carried out with T.3 than with dried thyroid In addition, since the therapeutic response is evident within 2–3 days, the effects are much more readily appreciated by the patient. A similar test using thyroid extract would take a few weeks and the patient might hardly be aware of the improvement. If heart failure occurs, the effects of medication are much more rapidly stopped when T.3 has been used.

Congenital deafness associated with goitre

Morgans and Trotter (1958) have described two further examples of this rather rare condition, to which attention was first drawn in Great Britain by Russell Brain in 1927 It is of especial interest because there have been many reports in the literature that where goitre was endemic cretins and also deaf mutes were found. The radioactive iodine studies in the two siblings described by Morgans and Trotter showed a high 24-hour uptake and part of the dose was dischargeable by perchlorate. This suggests that [illegible]

goitres.

Cretins

Workers in Ann Arbor (Lowrey and his colleagues, 1958) have reviewed the findings in 49 cretins (of all types) in an attempt to offer early diagnostic criteria of congenital hypothyroidism They found that the presenting signs and symptoms were lethargy, constipation, feeding problems, choking, failure to gain weight, failure to gain interest, respiratory difficulty, umbilical hernia and skin changes Some or all of these were noted by the third month and the incidence of thyroid disease was much greater in this group Nine per cent of them were examples of familial hypothyroidism, 75 per cent had evidence of complete absence of thyroid

tissue, 8 per cent developed or were born with goitres and had errors of iodine metabolism which could be determined by radioactive iodine study.

Thyroiditis

The three kinds of thyroiditis, Hashimoto's, de Quervain's and Riedel's, still continue to attract much attention (Taylor, 1955), by far the greatest interest being in Hashimoto's disease or lymphadenoid goitre.

Hashimoto's disease

Many centres have described their results in laboratory investigation of this condition and representative of these reviews is that from the Glasgow workers (Goudie and his colleagues, 1957). Electrophoresis of serum proteins is still a useful method of showing the increased *gamma*-globulin fraction and the progress of the patient on treatment is well reflected by the fall in this fraction. Now that the condition is being recognized more frequently, many patients are seen in the early stages of the disease when it is usual to find an enhanced radioactive iodine uptake. This may at first be misleading since it can suggest a mild hyperthyroidism, especially as some of these patients develop the symptoms of an anxiety state. The additional test which Morgans and Trotter (1957) suggested is then of great value They showed that the organic binding of iodine in this condition was defective and that the giving of 100 or 200 milligrams of potassium perchlorate after the tracer dose caused a discharge of radio-iodine from the gland, pointing to the fact that it was present as iodide and not bound to protein. The normal person does not show any significant discharge of radio-iodine from the thyroid if potassium perchlorate is given.

In a previous review (Taylor, 1955) it was suggested that split-needle biopsy provided a valuable method of obtaining material from the thyroid for histological diagnosis in Hashimoto's disease. A further method has been described which provides a somewhat larger core of material; this employs a high-speed drill driven by compressed air (Morrison and Deeley, 1957). The drill rotates at about 20,000 revolutions per minute, and perhaps the only drawback to its use is the high-pitched squeal which it emits Remarkably little deformation of the tissue is caused because of the speed of the drill and, apart from the noise, this is undoubtedly a most suitable method for biopsy of the thyroid in suspected thyroiditis.

de Quervain's disease

de Quervain's or subacute thyroiditis has distinctive clinical and pathological features which distinguish it from Hashimoto's and Riedel's disease, but like them, until the present day, the aetiology has been quite obscure. The illness usually starts with pyrexia accompanied by pain radiating upwards from the neck to the ears and there is great discomfort on swallowing. The gland is swollen and tender and there is usually tachycardia, sweating and sometimes a tendency for the eyes to stare. Eylan, Zmucky and Sheba (1957) have described 15 such patients seen in Israel. They carried out repeated radio-iodine and protein-bound iodine studies and in 11 of the 15 cortisone or ACTH produced relief of all the symptoms and disappearance of the swelling within 72 hours. Seven of the patients showed a

return of the swelling and pyrexia after the end of the treatment, but all were fit and well 6 months later. There was a mild polymorphonuclear leucocytosis in three-quarters of the patients, with a raised sedimentation rate, usually above 50 millimetres in 1 hour (Westergren). Complement fixation tests for mumps were positive in 10 out of 11 patients and this suggests that in the recent outbreak of thyroiditis in Israel the mumps virus might very well have been responsible. It is hoped that further examination of patients in other parts of the world will show whether or not mumps is the cause of this condition on all occasions.

Riedel's disease

Invasive fibrous thyroiditis or Riedel's struma remains the rarest form of thyroiditis. Workers at the Mayo Clinic have recently reviewed their material seen over the last 36 years (Woolner, McConahey and Beahrs, 1957) and were able to find only 20 examples during this period, although approximately 42,000 thyroidectomies had been performed. This condition must therefore remain an extremely rare clinicopathological entity. The presenting complaint in their patients was a hard lump in the neck, occasionally associated with dysphagia or a sense of pressure. The disease could be unilateral or bilateral and extension into the other tissues of the neck was invariably present. They did not find the central adenoma, nodule or cystic cavity which other workers, especially Crile, have stressed. The surgical treatment in the hands of the Mayo workers consisted in wedge resection of the isthmus or, when the disease was unilateral, subtotal resection of as much of one lobe as was possible. The results of this treatment appeared excellent, but these workers offer no new theories as to the possible aetiology of the condition.

Cancer of the thyroid

This disease continues to attract far more attention than the number of cases seen would appear to just[illegible]

been exposed on the operating table or tissue removed had been examined by a pathologist. They stressed the fact, previously pointed out by the present reviewer, that survival is closely related to the histological type of tumour, and this remains the major factor in determining the prognosis. They observed concentration of radioactive iodine by metastases in only 7 of their patients. Their figures reveal that the majority of thyroid carcinomas did not arise in previously nodular glands; on 7 occasions hyperthyroidism was also present It is interesting to see that 3 out of their 8 young patients (those under 35 years of age) with carcinoma gave a history of ionizing radiation to the neck in childhood

Thomas (1957) reviews experimental work as well as investigations in man to show that thyrotrophic hormone (TSH) is likely to be an important factor in the genesis and progress of these lesions and that the simplest way of suppressing secretion of this hormone is the giving of large amounts of desiccated thyroid, thyroxine or T.3 by mouth Patients with well differentiated papillary and alveolar carcinoma of the thyroid may show arrest or even diminution in size of tumours

with such treatment. All surgeons should remember that after excising thyroid carcinoma, only good can arise from giving the maximum dose of thyroid which can be tolerated.

Walt, Woolner and Black (1957) have reviewed the small cell malignant lesions of the thyroid gland seen during the last 25 years; out of 30 of these 18 were lymphomas and 12 true small cell carcinomas. The average age of the patients was 56 years and 2 of the lymphomas arose in thyroids which were already the site of Hashimoto's disease. The prognosis for those having lymphomas was better, since vigorous surgical excision followed by deep x-ray therapy gave good long-term results, but all the patients with small cell carcinomas were dead within 19 months.

Radiation and the development of thyroid malignancy

As long ago as 1950 it was reported from the Memorial Hospital in New York that out of 28 children with proven thyroid cancer, 10 had received x-ray treatment to the thymus in infancy. Simpson and Hempelmann (1957) have provided much further information concerning the genesis of carcinoma in children treated with x-rays. The most surprising thing about their report is that the dose of x-rays may be minute so that it is difficult to see why it should be carcinogenic. The important fact which emerges from these reports is that radiation should be avoided at all costs in infants and children, and this applies not only to conventional radio-therapy, but also to the use of other sources of ionizing radiation such as isotopes

In adults, however, it appears that the tissues of the neck and in particular the thyroid rarely develop cancer as a result of exposure to x-rays. Goolden (1957) reviewed 24 cases of radiation cancer which occurred in the neck and of these only one arose in the thyroid gland. This is of particular interest as in the early 1920s many patients with thyrotoxicosis were treated by x-ray therapy and it might therefore have been expected that some of these would now be presenting with thyroid cancer. More recently Goolden (1958) has described three further examples of thyroid cancer in adults arising 18, 38 and 41 years after irradiation.

Thyroid and breast cancer

It is not generally known that in 1896 Beatson recommended not only the bilateral removal of the ovaries in the treatment of metastatic carcinoma of the breast, but also the administration of thyroid extract by mouth. Other workers over the years have also suggested that there was a connexion between hypothy-roidism and cancer of the female breast, Loeser (1954) strongly advocated the use of thyroid extract as a prophylactic measure against recurrence of breast cancer. In view of the somewhat tenuous evidence available, it is particularly interesting to read a paper by Edelstyn, Lyons and Welbourn (1958) from Belfast who carried out a careful assessment of thyroid function with radioactive iodine in patients with carcinoma of the breast. They found clear evidence that function of the thyroid gland was significantly lower in those who had blood-borne metastases than in those who had local or locally advanced disease. It would therefore appear rational to prescribe thyroid for patients with breast cancer at any stage of the disease.

Exophthalmos

Exophthalmos is still considered by most workers to result from disordered pituitary or hypothalamic function. Little evidence for or against the presence of Dobyn's exophthalmos-producing-substance (EPS) as a separate entity from the thyroid-stimulating hormone TSH has been forthcoming. A report of two cases by Freeman (1958) provides some evidence in favour of a pituitary origin for exophthalmos.

Freeman describes two patients who had hypothyroidism associated with malignant exophthalmos, pretibial myxoedema and gross finger clubbing At post-mortem examination one of these patients was found to have an eosinophil adenoma of the pituitary and the other to have eosinophil hyperplasia of the anterior lobe of the pituitary. He also describes a previously unpublished case report of a patient with similar findings who had an eosinophil adenoma.

Another interesting report which perhaps links together exophthalmos and the pituitary is that of Morgan and Mason (1958) who record the case of a young woman with typical Cushing's syndrome who developed malignant exophthalmos. They conclude that the primary lesion of Cushing's syndrome in this patient was in the hypothalamus or pituitary rather than the adrenals. Green (1958) has reported the dramatic resolution of malignant exophthalmos in a patient who was given acetazolamide, a drug which is occasionally of value as a diuretic, but is mostly used in the treatment of glaucoma. It will be interesting to see if others can repeat this work since it is well known that exophthalmos can resolve spontaneously.

THE PARATHYROID GLANDS

More clinicians appear to be alert to the possibility of parathyroid overactivity being the cause of renal stones, bone cysts and increased calcium excretion. The main difficulty in diagnosing the condition in the absence of obvious skeletal disease is that of obtaining accurate calcium estimations of the blood serum; at the same time the serum proteins should be estimated so that a suitable correction may be made when they are abnormal.

Ogburn and Black (1956) have reported 4 patients who had thyroid carcinoma and hyperparathyroidism. This is an odd association and is the more remarkable in that 3 of the 4 patients underwent an exploration of the neck primarily because of hyperparathyroidism and the thyroid neoplasms were only discovered accidentally. Two of the patients had a solitary nodule in the thyroid gland which, as stated earlier in this review, is a strong indication for thyroidectomy. None of the parathyroid adenomas found in these patients was palpable clinically; this is almost invariably the case.

Attempts have been made in the last few years to transplant parathyroid tissue into patients suffering from severe hypoparathyroidism. Sterling and Goldsmith (1956) grafted 3 patients with tissue obtained from infants less than 6 months of age. They anastomosed the blood vessels of the graft to the host and one of their patients was relieved for over 3 years and another for a year-and-a-half. Other workers (Escamilla and his colleagues, 1957) have tried a method of tissue culture

using parathyroid tissue which was gradually acclimatized to the patient's serum. The tissue was then finally implanted in the patient; the longest period of survival appeared to be about 9–10 months, but it is difficult to interpret their criteria of success. Rigdon and Mead (1956) used foetal parathyroid tissue obtained at therapeutic abortion and implanted this into the rectus abdominis muscle. They also had temporary success. Obviously the problem of homotransplants of endocrine tissue requires a great deal more work before it is solved.

THE ADRENAL GLANDS

Cushing's syndrome

Interest in Cushing's syndrome remains as active as ever and Montgomery and Welbourn's (1957) splendid review of their 13 cases has now been followed by another (Mason, Richardson and King, 1958) describing detailed pre-operative and post-operative study of 17 patients with this rare syndrome. The latter authors stress that the diagnosis and progressiveness of the disease ought to be established beyond doubt before adrenalectomy is undertaken and it is most important to correct any electrolyte disturbances before surgery. In common with other workers they recommend total adrenalectomy for young patients and for those with rapidly progressive disease, but in older patients they prefer subtotal adrenalectomy. In the younger patients the operation was carried out in one stage, but in older patients in two stages. The present reviewer has treated all his patients, both young and old, by a one-stage operation, preferring subtotal adrenalectomy and only on one occasion performing total adrenalectomy in a young patient with very active disease

There is no doubt that the most important item in the immediate preparation of these patients for operation is the administration of sufficient cortisone to maintain the excessive level of glucocorticoids to which the patients have become accustomed as a result of their adrenal hyperplasia. It should be remembered that cortisone by mouth is rapidly absorbed, while that injected intramuscularly forms a depôt available over a period of time. These patients should therefore be given adequate intramuscular dosage before operation to tide them over the difficult post-operative period They may pass through the operation without any major disturbance, only to collapse on return to the ward; it is therefore necessary to have adequate supplies of hydrocortisone hemisuccinate and noradrenaline readily available. Post-operatively there is a special liability to infection so that it is justifiable to use prophylactic wide-spectrum antibiotics as these authors suggest. There is a tendency to spontaneous thrombosis and thus clotting in the deep leg veins and subsequent pulmonary embolus is an added hazard.

Cushing's syndrome in childhood is excessively rare, only about 30 cases having been reported Jackson and his colleagues (1958) in South Africa report a further example of this syndrome in a coloured girl aged 2½ years. As with most of the other childhood examples of this disease, the adrenal tumour was malignant. Their patient was fortunate in that the tumour could be excised and the post-operative result was a return to normal Another rarity is the development of Cushing's syndrome as a complication of carcinoma of the bronchus and

Harrison and his colleagues (1957) have added another example to the three previously described.

Adrenogenital syndrome

A very interesting account of the suppression of adrenocortical activity by means of oral cortisone is provided by Greenblatt and his colleagues (1958), the title of the article being rather misleading in that it only refers to menstrual disorders. The subject is well reviewed, however, and is a natural development of Wilkins' work first published in 1950 in which he described how the administration of cortisone to patients with the adrenogenital syndrome would often return them to normality, not only removing the virilizing effect but also lowering the blood pressure It is important to recognize congenital adrenal hyperplasia at birth, for if it is not immediately treated with cortisone the baby is likely to die In older patients if any virilization or menstrual disorder is detected, search should be made for raised urinary 17-ketosteroids, 17-ketogenic steroids, pregnandiol and pregnantriol A trial course of cortisone may be both diagnostic and therapeutic. Other menstrual disorders may result from the Stein Leventhal syndrome when wedge resection of the cystic ovaries is extremely beneficial and may permit a normal pregnancy. The authors suggest that the pituitary is preoccupied with the production of ACTH in the adrenogenital syndrome and this leads to the depletion of its store of materials for making gonadotrophins.

Macfarlane (1958) has reviewed the natural history, prognosis and treatment in 55 cases of cancer of the adrenal cortex; he stresses the importance of early radical surgical excision and points out that radiotherapy and chemotherapy are of value only in palliation.

Aldosteronism

An enormous literature has grown up concerning the secretion and control of aldosterone in the body since the substance was first described by Simpson and Tait in 1952 This steroid is almost exclusively concerned with the maintenance of electrolyte balance and, weight for weight, aldosterone is about 25 times more effective than deoxycortone in promoting sodium retention Almost all the examples of primary aldosteronism in man have been due to the presence of a tumour of the adrenal cortex and not to bilateral hyperplasia. This is exactly the opposite of the findings in Cushing's syndrome where hyperplasia is much more common than tumour Milne, Muehrcke and Aird (1957) reviewed their experience in treating two cases of primary aldosteronism due to adrenal cortical adenoma. The first patient gave a history of severe periodic paralysis for many years and had been diagnosed and treated as a case of "potassium-losing nephritis" due to chronic pyelonephritis. The second was virtually asymptomatic, but hypertension was present and there was biochemical evidence of potassium deficiency. Removal of the adrenal containing the adenoma has been attended with good results in both patients. It seems likely that more of these tumours will be discovered in the future and treated by adrenalectomy.

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ABSTRACTS RELATING TO THE ENDOCRINE GLANDS

The thyroid nodule

Autoradiographic studies

·atment, patients with puberty
ıld be given either desiccated
mouth daily. Thyroidectomy
suspected malignant changes.
Partial resection of both lobes and the isthmus must be carried out, for it is useless to enucleate single nodules unless toxic changes have supervened. When a nodule is suspected of harbouring a papillary carcinoma the whole lobe should be excised Total thyroidectomy is performed when follicular carcinoma is discovered.

Triiodothyronine

Clinical applications

Discussing the clinical applications of triiodothyronine

reached Care was taken not to precipitate an attack of angina pectoris. The patient's general condition began to show improvement and his mental state

Subacute thyroiditis

Mumps virus

EYLAN, ZMUCKY and SHEBA (1957) state that during the last 2 years the incidence of subacute thyroiditis in Israel has been particularly high. During this period there was also an increase in the incidence of mumps. It is believed that in some cases the two diseases were associated, for 10 of 11 patients with thyroiditis showed positive complement fixation reactions against mumps virus to a significant titre. Positive complement fixation tests to a titre of 1 : 80, or more, were taken as evidence of recent contact with the virus. In 2 cases a virus isolated from the thyroid gland was considered to be identical with the mumps virus. When baby hamsters were injected intracerebrally with specimens containing the infective agent, signs of encephalitis sometimes appeared 6–9 days later. Inoculation [illegible] yolk sacs and transference to the amniotic sacs of fertilized eggs even-[illegible]ch agglutinated human group-O erythrocytes Haemag-[illegible]ved from patients with subacute thyroiditis [illegible] and also [illegible]m mumps. Neck pain and mild pyrexia were usually the first c[illegible]te thyroiditis. Swelling and tenderness of the thyroid gland occurred within a few [illegible] Tachycardia, sweating and a tendency for the eyes to stare were often encountered. Symptoms were soon alleviated after the administration of corticotrophin or cortisone. Radio-iodine and protein-bound iodine studies revealed results which were compatible with the diagnosis of subacute thyroiditis Biopsy of the thyroid gland was performed in 4 cases. Histological examination revealed inflammatory cells, giant cells and disruption of the acinar pattern.

Riedel's struma

WOOLNER, MCCONAHEY and BEAHRS (1957) point out that Riedel's struma, or invasive fibrous thyroiditis, must be distinguished from granulomatous thyroiditis and the fibrous type of struma lymphomatosa. The fibrotic process in Riedel's struma may affect the entire thyroid gland. In some cases, however, the process is confined to one lobe or to a portion of a lobe. The affected zone is fibrous and woody. The area of fibrosis extends beyond the capsule of the gland. Extra-thyroidal extension is not a feature of either granulomatous thyroiditis or the fibrous type of struma lymphomatosa. The diagnosis should not be made on gross inspection alone. Further evidence must be obtained by histological examination, preferably by immediate frozen section. Microscopically the gland structure is almost completely destroyed In contrast to granulomatous thyroiditis, there is no giant-cell reaction. The authors report on 20 cases of Riedel's struma which were encountered in a period of 36 years. During this period about 42,000 thyroidectomies had been performed Thus the incidence was only 0 05 per cent. The disease occurred in 16 women and 4 men in the age-range of 30–67 years, and the history revealed that the goitre had been present for periods varying from 2 months to about 5 years No patient experienced pain in the region of the thyroid gland Symptoms of obstruction were not common. At least 4 patients were myxoedematous The presence or absence of myxoedema depended upon the extent of the disease in the thyroidal parenchyma. In patients with disease of both lobes of the thyroid gland surgical treatment consisted in wedge resection of the isthmus. A subtotal resection was performed in cases of unilateral disease. Central adenomas, involutionary nodules and cystic cavities were rarely encountered in the gland tissue. Freeing the trachea provided a satisfactory guarantee against the development of obstructive symptoms. The resected tissue always contained striated muscle, for no line of demarcation could be distinguished between the contiguous muscle and the area which formerly had been occupied by the thyroid gland.

Thyroid cancer

KILPATRICK and his colleagues (1957) give an account of a series of cases comprising 20 men and 80 women suffering from carcinoma of the thyroid gland. The mean age of the whole series of patients was nearly 55 years. The cases were investigated at the Sheffield

... for Radiotherapy and were derived from areas where the incidence of ... the age of ... k in child- ... older age ... for goitre ...

with papillary carcinoma. Apart from the predilection for follicular carcinoma to produce bony metastases, the groups showed no striking differences in the development of these deposits.

Dependency

... of the thyroid ...

In rats cancer of the thyroid gland can be produced by administering a goitrogen, and the latent interval can be diminished by the concomitant administration of a carcinogen ... Tumour formation is increased by employing a carcinogen.

thyroid hormone therapy in the management of 10 patients with papillary and alveolar carcinoma of the thyroid gland and found that many tumours were dependent The ...

Small-cell malignant lesions

There was a predominance of women in this group. Unequivocal struma lymphomatosa was found in 2 of 14 cases of lymphoma. In 10 cases of the latter disease the goitre alone precipitated the patient's decision to seek advice. Hoarseness and dysphagia were common symptoms experienced by patients with carcinoma. As for the macroscopic appearance of the thyroid gland, in some cases of lymphoma the mass was well circumscribed and the cut surface was fleshy, uniform and somewhat yellowish. Eight cases showed infiltration of the perithyroidal tissues. Histologically the lymphomas fell within the category of lymphosarcoma or reticulum-cell sarcoma. The histological pattern of the carcinomas lacked the completely uniform appearance of the lymphomas. The cells were arranged in nests, clumps or alveoli surrounded by fibrous stroma. Furthermore, the cells were relatively more hyperchromatic and more variable in size and shape. The lymphomas grew in such a manner as to leave little thyroid tissue within the tumour. A zone of lymphocytic thyroiditis surrounded the main mass of the tumour. In contrast, the carcinomas tended to leave islands of normal-looking thyroid tissue and there was less lymphocytic infiltration round the lesion. Whereas no patient with carcinoma survived longer than 19 months, 6 patients with malignant lymphoma were free from symptoms for a period of at least 4 years after treatment had been instituted. The authors point out that, in cases of lymphoma of the thyroid gland, an apparent cure may be effected by means of unilateral or bilateral thyroidectomy. Radiotherapy should be employed after surgical excision. The operation should be attempted even when the gland is attached to the muscles or to the peritracheal and peri-oesophageal tissue. In any case, surgery is required in order to confirm the diagnosis. Tracheotomy should be performed as a prophylactic measure in the management of patients with advanced disease.

Cushing's syndrome

Management and metabolic aspects of adrenalectomy

MASON, RICHARDSON and KING (1958) give an account of pre-operative and post-operative studies which were made in 17 cases of Cushing's syndrome and in a case of adrenal carcinoma Pre-operatively abnormal glucose-tolerance curves were obtained in the majority of cases. No correlation was established between the rate of protein catabolism and potassium depletion. An abnormally high serum-sodium level was detected in 5 cases Post-operative balance studies were made in 7 cases. The changes in nitrogen, potassium and sodium balance were similar to those found after any type of operation. Usually a positive nitrogen balance was established by the seventh to twelfth day. The degree of nitrogen loss was not directly related to the dose of cortisone. The authors point out that the diagnosis and progressiveness of the disease must be definitely established before [illegible] from the benign transient [illegible] striae distensae. [illegible] ntial diagnosis is also required from the adreno-genital syndrome of women The electrolyte disturbance must be corrected prior to the operation, but at present there is no adequate method of restoring protein. As the patients have become accustomed to an excessive level of glucocorticoids it is important to maintain the level by means of adequate doses of cortisone The drug must be injected intramuscularly in order to ensure its absorption during the operation and post-operative period. The dose is reduced gradually. During the immediate post-operative period the water and sodium intake must be reduced, but the amount of salt is increased later on. Total adrenalectomy is recommended in the management of younger patients and of those with rapidly progressive disease. Subtotal adrenal[illegible] is preferred for older patients. The operation is performed in one stage in younger [illegible] itions include ileus, [illegible] nal failure. Hydro[illegible] the last-mentioned condition.

Cancer of the adrenal cortex

Natural history, prognosis and treatment

as Cushing's syndrome and the androgenic type of reaction. In more than 50 per cent of cases symptoms had been present for at least 6 months. Confirmation of the diagnosis was obtained from urine estimations of 17-ketosteroids and from Patterson's test for dehydroepiandrosterone. Only 13 patients survived for 3 years or more, and this group

atrophy of the contralateral adrenal gland care was taken to administer full doses of steroids during and after the surgical treatment of patients with hormonal tumours. Radiotherapy was not considered to be of great value in the management of the cases.

Primary aldosteronism

MILNE, MUEHRCKE and AIRD (1957) state that primary aldosteronism was first described by Conn in 1955. The basic cause of the condition is an adrenocortical tumour which secretes excessive amounts of aldosterone, thereby producing increased urinary loss of potassium with sodium retention. The resultant potassium depletion produces impair-

urinary loss of potassium. The loss is detected by employing a potassium-balance test and adding potassium supplements. If the plasma-potassium level remains low despite

bined with tomography supplies valuable information. An increased production of mineral-corticoids may be found, but this finding is of no assistance in distinguishing primary from secondary aldosteronism.

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THE CARE OF FLEXOR TENDON INJURIES IN THE HAND

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Numerous papers have been written upon the treatment of flexor tendon injuries in the hand since the subject was discussed in *British Surgical Practice* in 1949 It is opportune to consider how surgical opinion has altered during the past decade These injuries are commonplace and can and often do lead to serious disability Unfortunately, consistently good results are notoriously difficult to achieve even in the practice of surgeons experienced in this work. It is no longer of interest to obtain the occasional perfect result, for as Rank and Wakefield (1952) stated, "The day has passed when odd successes with flexor tendon repair call for any comment of admiration". It is of more concern to establish a plan of treatment which can be expected to offer a good general standard of result. It is important also to know the function that can be anticipated in an individual case so that sound advice may be offered. It should not be forgotten that the divided tendon, the effect of which is obvious, does not appear to the patient to present the difficult reconstructive problem that we know it to be Our advice is more often than not accepted without question and it is easy to fall into the error of being uncritical of our ability

There is a great difference between the treatment and prognosis of a flexor tendon division in a single finger caused by a sharp instrument and the case complicated by scar, joint stiffness and nerve injury, or involving multiple divisions in a severely mutilated hand. In the first instance, restoration to normal or near normal is expected, but in the latter case the object is to restore some prehension, however poor, to an otherwise useless hand It is necessary to consider these two problems separately.

DIVISION WITHIN THE DIGITAL THECA

Flexor digitorum profundus

It is generally accepted that division of flexor digitorum profundus beyond the level of sublimis attachment may be treated by immediate suture with a good expectation of success The less common example of division in the proximal part

the use of large supplements of the mineral the evidence is in favour of primary aldosteronism. Percutaneous renal biopsy may be of diagnostic value, unless pyelonephritis is present. Provided the result is unequivocally positive, peri-renal oxygen insufflation combined with tomography supplies valuable information. An increased production of mineral-corticoids may be found, but this finding is of no assistance in distinguishing primary from secondary aldosteronism.

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of reconstructive surgery; the injunction against working in a potentially contaminated field. If you play with fire, you will eventually get burned. The primary treatment must be such that a secondary procedure is not compromised . . . Until someone develops a better technique and reports it with a comparable series of consecutive cases, I believe that this (simple wound closure and secondary reconstruction) should be our teaching and practice".

In experienced hands secondary tendon grafting in fingers in good condition can be expected to give 75 to 80 per cent acceptable results, and it does not appear that we are yet in a position to depart from the accepted teaching of skin suture and tendon graft later, as a general principle.

Flexor pollicis longus

Primary suture yields good results when division has occurred in the distal part of the thumb. "If the surgeon must do a primary repair, let him do it in the thumb rather than in a finger. However, even the end results of thumb repair are far from ideal if the suture line is directly opposite the metacarpo-phalangeal joint or opposite the proximal phalanx" (Goldner, 1958).

The less common cases of division deep in the thenar eminence may also be repaired by primary suture, but the exposure is difficult as the tendon lies in close proximity to the digital nerves and the motor branch to the thenar muscles. The results of secondary grafting are very good, yielding a success rate of 85 to 90 per cent. It seems reasonable to conclude that if the conditions at the time of primary treatment are not ideal, and this includes the experience of the surgeon and the theatre facilities, it is wiser not to attempt primary repair in this particular region of the thumb.

DIVISION IN THE PALM AND AT WRIST LEVEL

Flexor digitorum profundus and sublimis in the palm

Tendon divisions in the palm, that is, between the distal border of the flexor retinaculum and the distal palmar crease, do not present the difficulties encountered in the finger. Immediate suture gives good results, provided the wound conditions are favourable. It is advisable to confine the repair to profundus, for there is a risk of cross-union when both tendons are sutured at the same level, thus limiting the flexion action to that of sublimis When the patient is seen at a later stage it is not uncommon to find that retraction and muscle shortening make it impossible to secure end-to-end apposition of the tendon ends. This difficulty can be overcome by the insertion of a bridge graft taken from the sublimis tendon (Fig. 38).

Tendon divisions at the wrist level

There is little to add to the views expressed in *British Surgical Practice* except to emphasize the importance of primary repair. Brilliant results follow a carefully performed primary suture but delay leads to secondary shortening of muscle necessitating the use of multiple bridge grafts to close the gaps.

of the finger with an intact sublimis is best treated by skin suture only and subsequent late repair.

If the patient is seen late, it is unlikely that suture will be successful unless the division has occurred close to the tendon insertion and the proximal end has not retracted appreciably. There is a choice of three operative procedures—arthrodesis of the terminal joint, tenodesis of the profundus tendon or restoration of function by a tendon graft. Analysis of 22 cases treated by tendon grafting (Pulvertaft, 1956) showed that in 80 per cent of cases a useful result was obtained. In no case did any harmful effect result from operative intervention. The author considers this to be the operation of choice for the index and middle fingers of the average adult patient because of the important thumb-finger pinch. For those persons whose work requires accurate finger tip action it is justifiable to graft any of the four fingers. The labourer is usually more concerned with a quick return to work and is not appreciably affected by inability to move the finger tip—for him, arthrodesis or tenodesis is the wiser choice. Children must be offered the possibility of normal function; for them there is no time problem, their future occupation is unknown and they yield a high rate of success. For these reasons the author believes a tendon graft should be advised for children.

The operation is no more difficult than tendon grafting for combined sublimis and profundus divisions but it should be appreciated that it is an operation of some magnitude for a comparatively minor disability. It should, therefore, only be undertaken by surgeons of experience who are confident of their technique. The graft needs to be of small calibre and plantaris is ideal for this reason. Plantaris is present only in some 60 to 70 per cent of persons and if it is absent the extensor tendon of the fourth toe is used. The sublimis tendon is not removed unless itself damaged and adherent, and the graft should follow the natural course of the profundus tendon.

Flexor digitorum profundus and sublimis

"Poor results the world over follow sutures of flexor tendons in what is called 'no man's land', that is, between the distal crease in the palm and the middle flexion crease in the finger" (Bunnell, 1956).

This opinion was reached by Bunnell as the result of seeing many poor results of primary and secondary suture of tendons in this region. Not only were the results poor, but the prognosis of subsequent grafting was made worse on account of secondary scarring. Most surgeons would agree with Bunnell that the treatment of choice is primary skin suture and secondary tendon grafting, but there are a few experienced men who think otherwise. The Chicago school, Koch, Mason and the late Harvey Allen; Posch of Detroit and Verdan of Lausanne are among those who consider there is a case for immediate suture of profundus alone when performed under ideal conditions. There are others who prefer a primary tendon graft on the grounds that better results can be obtained than by primary suture or by secondary grafting. Koch (1953) commented "I would be reluctant to consider the use of a tendon graft immediately after division of the flexor tendons within the digital sheath". Boyes (1958) stated, "One other reason that primary grafting cannot be accepted is that it violates one of the fundamental principles

of removing plantaris with a long tendon stripper using the distal incision only. This tendon is of uniform calibre throughout its length, and is sufficient to provide grafts for two digits.

The exposure

The basic principles are that a full exposure be made and the incisions placed in the immobile parts of the skin (Fig. 39) The operation can be adequately performed without exposure of the base of the finger when this region is free of scar, but it is impossible to remove scar through a limited approach. The principles of plastic surgery are now so widely known that it is inexcusable to use an incision which leads to secondary skin contracture.

The index and little fingers are exposed by an exact mid-lateral incision which is

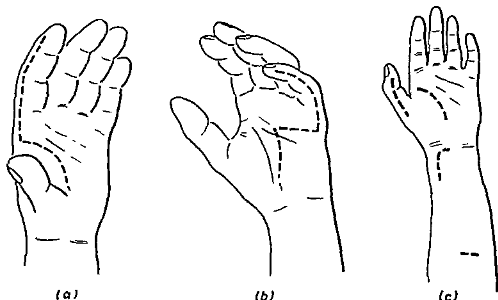


FIG 39 —(*a*) Incision for exposure of the index finger and palm, (*b*) incisions for [illegible]

carried proximally as far as the appropriate palmar crease and extended into the palm along this crease. In the middle and ring fingers, three separate incisions are usually employed; mid-lateral in the finger, transverse in the distal palmar crease and along the thenar crease line for the proximal suture. When scar tissue needs to be cleared from the base of the digit, the finger and distal crease incisions are joined and a flap raised to expose the anterior aspect of the metacarpo-phalangeal joint.

The digital incision is carried straight down to the theca leaving the vessels and nerve in the anterior flap (Fig. 40). Care is needed to isolate the digital nerves to the radial side of the index finger and to the ulnar side of the little finger as these

THE OPERATION OF TENDON GRAFTING

The graft

Palmaris longus, extensor digitorum longus and plantaris are the tendons of choice. Flexor digitorum sublimis is unsuitable except for use as a short bridge graft. At one time it was thought advisable that a considerable surround of paratenon should be removed with the graft but this does not appear to be necessary, except perhaps for use in a digit which has much scarring Palmaris longus is removed through two small transverse incisions and it is found that a thin coating of paratenon comes with the tendon. Extensor digitorum longus is

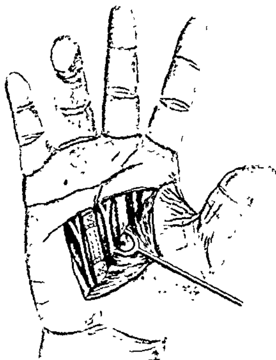


FIG. 38 —A graft taken from sublimis to bridge a

C. Rob and R. Smith. London, Butterworth)

usually obtained through a full exposure owing to some difficulty in freeing it, but with care it can be removed through three transverse incisions. The presence of plantaris cannot be determined until an exposure has been made; if it is absent a graft is taken from extensor digitorum longus Two small incisions are required, one on the medial side of the tendo Achillis and the other placed three finger-breadths posterior to the medial margin of the tibia in the mid-calf. The tendon lies between the gastrocnemius and the soleus muscles and may be found by lifting the medial border of gastrocnemius. Brand (1958) has a neat and speedy method

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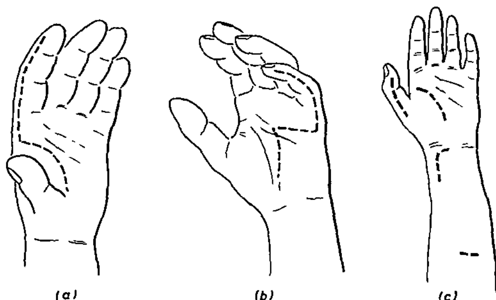


FIG 39 —(*a*) Incision for exposure of the index finger and palm, (*b*) incisions for exposure of the little finger and palm—the two incisions may be joined, (*c*) incisions for exposure of the thumb, palm and forearm—the proximal incision for removal of palmaris longus is also shown. (Reproduced by courtesy of the Editor of *Journal of Bone and Joint Surgery*.)

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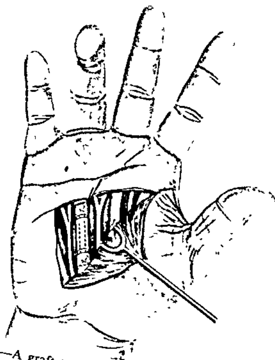


FIG 38.—A graft taken from sublimis to bridge a gap in profundus. A continuous wire passes through the graft. The wire has not yet been tied. (From *Operative Surgery*, vol 6, pt. x, p 40 Ed. by C. Rob and R. Smith. London, Butterworth.)

usually obtained through a full exposure owing to some difficulty in freeing it, but with care it can be removed through three transverse incisions. The presence of plantaris cannot be determined until an exposure has been made; if it is absent a graft is taken from extensor digitorum longus. Two small incisions are required, one on the medial side of the tendo Achillis and the other placed three finger-breadths posterior to the medial margin of the tibia in the mid-calf. The tendon lies between the gastrocnemius and the soleus muscles and may be found by lifting the medial border of gastrocnemius. Brand (1958) has a neat and speedy method

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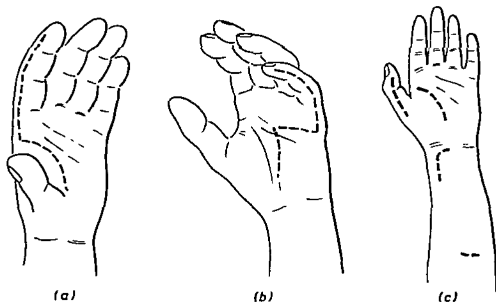


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The digital incision is carried straight down to the theca leaving the vessels and nerve in the anterior flap (Fig. 40) Care is needed to isolate the digital nerves to the radial side of the index finger and to the ulnar side of the little finger as these

nerves cross the operation field. Some surgeons prefer to raise a more superficial flap which does not include the vessels and nerve.

The operation for flexor pollicis longus grafting requires three incisions: mid-lateral in the thumb, along the thenar crease and proximal to the wrist. The thenar crease incision is deepened until the two digital nerves to the thumb are found; between them lies the flexor sheath. The nerve to the radial side of the index finger is also seen and retracted towards the palm The divided tendon is usually adherent

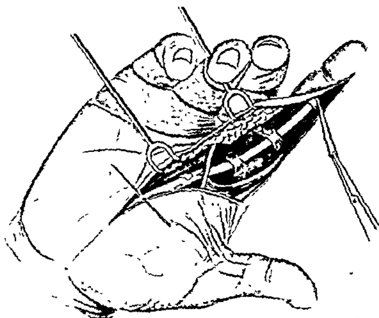


FIG 40.—A stage in the tendon graft operation. The digital nerve crosses the field. The profundus tendon is held by a transfixion needle (*From Operative Surgery*, vol. 6, pt. x, p. 41. Ed. by C. Rob and R. Smith. London; Butterworth)

at this site and careful dissection is needed to free it and clear the area of all scar tissue.

The digital theca

The theca is removed with the exception of three bands which are preserved as pulleys in front of the metacarpo-phalangeal joint, the mid-point of the proximal phalanx and the mid-point of the middle phalanx. When the theca has been severely damaged, or is non-existent as in the case where a previous graft has been performed and failed, new pulleys are constructed from a short length of graft. Bow stringing of the graft will occur unless adequate pulleys are present and may ruin an otherwise satisfactory result.

The suture

The suture material should be fine and of a nature which causes the least possible tissue reaction. Those who have seen the foreign body granuloma which forms

around catgut or thick silk wonder why these materials are ever used for the delicate surgery of the hand. Mukherjee and Douglas (1952) studied the relative reactions set up in nerve tissue by nylon, Terylene, human hair, silk and stainless steel wire and demonstrated clearly that wire is the only material which causes little or no reaction. It has been found in practice that there is little to choose between fine silk (No 4/0–6/0) and stainless steel wire and the choice is largely one of personal preference. It has always been the writer's custom to use single strand wire; 40 B W.G for the main suture and 43 B.W.G. (No 6/0) for auxiliary stitches. Kinking must be avoided and the wire is tied by a reef knot, the ends being cut off flush with the knot.

It is simpler to perform the proximal suture first and adjust the tension at the distal attachment, but this again is a matter of personal preference and some surgeons reverse the procedure There is universal agreement that the tension should cause the digit to lie in a position of slightly more flexion than it would normally assume under anaesthesia Grafts do not shrink, but the muscle may stretch out a little with use. "A slack graft is not a good graft" (Morley, 1956)

The proximal junction of a small graft to a larger motor tendon is best accomplished by an interlacing suture completed by a fish tail enclosure of the graft by the slit tendon end. The junction is then surrounded by the lumbrical muscle if profundus, as is usually the case, has been used as the motor. Brand (1958) has devised a particularly tidy method of spreading plantaris to cover the suture region. The distal attachment may be performed by one of several different techniques—the Bunnell withdrawal suture, graft to profundus tag or the passing of the graft through a transverse tunnel in the phalanx The Bunnell suture is the neatest and the tunnel method is the most secure

The after-care

A review of 149 consecutive cases (Pulvertaft, 1956) of flexor tendon grafting in the fingers and thumb showed that there was little difference in the results obtained by gentle active movement commenced a few days after operation and splintage for 3 weeks. Early mobilization demands the careful supervision and protection from accidental strain which can only be given to an in-patient. It is now the writer's practice in the majority of cases to splint the digit in approximately 75 per cent flexion for 3 weeks followed by 1 week, or 2 weeks in children, of protection by an adhesive elastic band stretching from the digit to the forearm. It is easier to overcome adhesions in flexion after the removal of splintage than it is to improve the flexion range. The use of elastic traction will assist the return of extension, but there is no effective way of obtaining flexion apart from the patient's own exercises.

SPECIAL PROBLEMS

Age

It has never been the writer's practice to perform tendon grafts in patients under the age of 3 years, so he cannot speak with personal knowledge of the results obtained in infancy. No extensive series of this age group has been published to his knowledge. The technical difficulties of the operation in a tiny hand, and the

shorter operative time at our disposal, combined with the lack of co-operation during the after-care period have seemed sufficient reasons for deferring treatment until the child is older—even until the age of 4 or 5 years.

This delay raises the question of how long a period may be permitted between injury and definitive repair. The proximal part of the tendon invariably becomes attached and although some retraction and shortening of muscle is inevitable, there is usually sufficient motor function remaining to give a useful range of



FIG. 41.—The result obtained from a plantaris graft to replace divided flexor sublimis and profundus tendons of the middle finger Injury—4 years of age. Operation—14 years of age The profundus of the injured finger was used as the motor. Splintage 3 weeks

movement, even after a delay of several years (Fig. 41). The distal part of the tendon within the theca remains unchanged and this has an important practical effect when the injury has occurred in childhood. The tendon and the theca do not grow in size and there may be difficulty in forming pulleys from the existing theca to accommodate the graft New pulleys may have to be constructed. This is another good reason for using the thin plantaris tendon in these cases. If it is found that the original muscles are useless, it is justifiable to use the sublimis of an adjacent finger as a motor.

Nerve Injury

When both digital nerves are divided in addition to the flexor tendons, it is

advisable to repair the nerves first and await some return of sensation and autonomic function before performing a tendon graft Grafts do badly if the finger lacks nerve function and in any case a moveable finger with complete lack of sensibility is of little value except in the grossly mutilated hand. Division of one digital nerve is not a contra-indication to tendon grafting

Joint stiffness

It is of little avail to graft a finger which has poor passive range at the proximal interphalangeal joint. Movement will not improve beyond the limits imposed by the joint restriction and the result will be disappointing Severe joint stiffness combined with flexor tendon division in a single finger is an indication for amputation.

Severe mutilation

The indications for late tendon reconstruction in a hand with loss of other digits or some general joint stiffness are less strict than for the single finger in an otherwise normal hand The restoration of some active movement—even if it is only half the normal range—may be of the greatest value to the patient Severe scar contracture may require skin and deep tissue replacement by the appropriate use of skin flaps before tendon repair is considered Joint stiffness is usually due to shortening of the capsule and particularly of the collateral ligaments. It is possible to improve movement very considerably at the metacarpo-phalangeal joints by capsulectomy if the joint surfaces are uninjured, but the stiff inter-phalangeal joint is a problem which can rarely be overcome.

Each case is a matter for careful appraisal and discussion with the patient. Total or severe loss of hand function is a disability which fully justifies a programme which may be lengthy and tedious if it can offer a reasonable expectation of improvement.

V CAUSES OF FAILURE

Assuming the general state of the finger is satisfactory—full passive mobility, absence of skin contractures and normal nerve function—it should be possible to obtain excellent results in all cases of tendon grafts Unfortunately, this is not the case and it is instructive to consider the possible causes of failure.

Tendon grafting is an operation which demands precise and gentle work, if the standard of workmanship is mediocre the result will be poor It is important that the surgeon should not be tired, nor should he be pressed for time The instruments need to be carefully chosen and all are small and delicate—the tissues are retracted with small skin hooks and bruising or crushing of the tissues is avoided

Final haemostasis must be satisfactory—a few minutes patience after removal of the tourniquet to allow the inevitable oozing to cease is a discipline which is of real practical value

Undoubtedly the most common cause of failure is owing to adhesions which become so dense that they will not stretch to allow a gliding motion of the graft. Adhesions between graft and surrounding tissue are inevitable, and, indeed, are

necessary for the re-vascularization of the graft, but these adhesions must be kept to the minimum by attention to the points of detail which have been mentioned. It is very uncommon for the graft to rupture or for the suture to give way, and should these disasters occur there has probably been a fault in the operative technique. In the occasional cases which come to tenolysis it has been instructive to find that the graft is usually in perfect condition but is linked to the side walls of its tunnel by well-defined adhesion bands. It may well be that cortisone would be beneficial after tendon grafting as it is after tenolysis, but there is the fear that healing of the tendon junction may be delayed and lead to rupture.

Lack of co-operation during the after-care will naturally prejudice the result and it is wise to explain the nature of the operation and the expected course of events when the patient is first seen. It is unfortunate if the patient is given the impression that the finger will be fully recovered in a matter of a few weeks. He will be disappointed and his enthusiasm will wane. Personal supervision and constant encouragement over a period of months may be necessary.

Every case of divided flexor tendons in the hand is a challenge to the surgeon. The author is convinced that the usual cause of failure to secure a good result under favourable conditions is our own departure from the strict and high standards that are essential to success.

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DISEASES OF MUSCLE

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Skeletal muscle forms approximately 45 per cent of the weight of an adult man, but diseases of muscle seldom occupy more than a few pages in textbooks of medicine or pathology. This disparity is partly due to the relative rarity of primary muscular disease, but also partly to ignorance which increased interest and new techniques have begun to dispel. The author is conscious that he is reviewing a medical subject in a surgical volume and aspects of interest to the surgeon will be stressed. No attempt can here be made to enter into the more controversial aspects, nor can the whole field be covered. The reader is referred to the textbook by Adams, Denny-Brown and Pearson (1954) and to a discussion on the most modern views of muscle physiology in the context of muscle disease by Bennett and his colleagues (1958)

MUSCULAR DYSTROPHY

Classification

Laudable attempts have recently been made to simplify the traditional eponymous classification of muscular dystrophy. In the absence of other known distinguishing features classification must be on clinical grounds, with the primary object of providing a reasonable basis for prognosis in a given case It must also be hoped that clear distinction of different "diseases" may eventually be of some value in the elucidation of the responsible biological fault

Tyler and Wintrobe (1950), Stevenson (1953) and Adams, Denny-Brown and Pearson (1954) have all attempted to classify the bulk of cases of muscular dystrophy into two groups With differences of detail these authors recognize first a group with sex-linked recessive inheritance, almost confined to males, of early onset and very bad prognosis; secondly, a group with either recessive or dominant inheritance, of even sex distribution, later onset and a much better prognosis. The first group approximates, of course, to pseudo-hypertrophic muscular dystrophy, although pseudo-hypertrophy is neither an essential nor an exclusive feature. Walton and Nattrass (1954) considered this classification too simple and divided the second group into facio-scapulo-humeral and limb girdle types, the important distinction being that involvement of the facial muscles nearly always implies a prognosis good both for life and for continued mobility.

These classifications do not include the myotonic forms, dystrophia myotonica and the much rarer myotonia congenita. At first sight it seems hardly justifiable to include the latter condition with the dystrophies, as the patients are often

extremely muscular and powerful, with extensive myotonia as their only disability. In the dystrophic form the patients are weak and wasted, with only trivial myotonia and often the additional features of cataract, baldness and testicular atrophy. Although most cases run true to type, it must be accepted that the two conditions are closely linked and that a patient may develop dystrophic features after appearing for many years to be an example of pure myotonia (Maas and Paterson, 1950)

Kiloh and Nevin (1951) drew attention to a rare form of muscular dystrophy involving the external ocular muscles but sometimes also involving the muscles of the shoulder and even the pelvic girdle. The existence of localized and apparently non-progressive forms of dystrophy, a matter of some theoretical and practical importance, has been shown by Walton (1956b) who described dystrophy confined to the quadriceps.

Little has been added to the classical descriptions of the more common dystrophies Walton and Nattrass (1954) have emphasized that it is in the Duchenne or pseudo-hypertrophic form that severe muscular contractures and skeletal deformities occur. As prognosis for life is very bad, heroic measures for the surgical correction of such deformities are not indicated. A further point against surgical correction is that confinement to bed frequently appears to accelerate the progress of the disease.

Aetiology

Although sporadic cases occur, as in any disease that may be recessively inherited, muscular dystrophy is clearly genetically determined. Dent has expressed the view that all hereditary diseases are the expression of biochemical defects It is natural, therefore, that much attention should have been paid to attempts to discover metabolic abnormalities Unfortunately, such abnormalities as have been discovered appear to be inconstant or non-specific, and related to muscle breakdown or lack of muscle bulk rather than to the causative process. Urinary creatine is increased (Cumings, 1953) and pentose has been found in the urine by Tower, Peters and Pogorelskin (1956) but not by Matthews and Smith (1953) or Walton and Nattrass (1954). The serum aldolase is elevated (Sibley and Fleischer, 1954), but this is also found in myositis Physiologists have been mainly concerned with muscle as a contractile tissue and have therefore contributed little to the understanding of muscular dystrophy, where contractile function does not appear to be primarily at fault, but rather the ability to maintain or regenerate muscle fibrils. At present it is not even known why a muscle fibre atrophies when deprived of its nerve supply and the more abstruse problem of the inborn defect in muscular dystrophy is quite obscure. Modern techniques of tissue culture, histochemistry and biochemistry are only now being deployed and great advances may be expected.

Treatment

The absence of any understanding of aetiology renders all attempts at treatment empirical and, without exception, futile Treatment can only be directed to making the best use of residual function, aided by physiotherapy, and the avoidance of contracture. Bed-rest should be avoided and, in intercurrent disease, should always be as brief as possible. The adult with arrested dystrophy may be greatly

helped in everyday life by such simple aids as lazy tongs, and surgical corsets may be required to support the weakened spinal muscles Despite grave disability many such patients remain in employment for many years.

MYOSITIS

Classification

This title covers a great variety of muscular diseases, including bacterial and parasitic infections. There is little new to report on these specific infections but considerable attention has been paid to the condition now usually termed polymyositis. Under this title are grouped widely differing clinical conditions with the common denominator of muscular weakness and some evidence of an inflammatory pathology. Attempts at classification are again hindered by lack of knowledge of causation and most classifications are based on more or less arbitrary clinical features. These features are of doubtful fundamental importance and are not reliable guides to prognosis. At present it seems unavoidable to regard these cases as forming a series, without clear subdivisions, but with the extremes barely recognizable as the same "disease". It is, of course, very probable that they are not, but at present this cannot be stated with certainty These extremes may perhaps be stated as the case of acute dermatomyositis with florid skin lesions, gross constitutional disturbance and relatively trivial muscular involvement, and the slowly progressive proximal muscular weakness and wasting extending over many years of chronic polymyositis.

Dermatomyositis and polymyositis

The acute, subacute and chronic forms of dermatomyositis have long been recognized and these have been reviewed, with particular reference to the symptoms of muscular weakness, by Matthews and Burne (1953). Briefly these may vary from rapidly advancing profound and generalized weakness, leading to death from respiratory paralysis, to chronic progressive weakness of the extremities, often with contractures and the skin lesions of scleroderma. Most authorities have emphasized that skin lesions may be trivial or fleeting, but polymyositis without skin involvement has been less well recognized. Here again there are many grades of severity and speed of progression. It is difficult to describe the clinical features briefly and for a detailed description the reader is referred to Walton and Adams (1958). Of particular importance is the possibility of confusion with muscular dystrophy Although the writer once committed himself to the statement that the two conditions could seldom closely resemble each other (Matthews and Burne, 1953), this is clearly incorrect. Nattrass (195[illegible]) has reported a series of cases diagnosed as muscular dystrophy but with subsequent recovery, and has stated that he considered the diagnosis to have been polymyositis. In view of the possibility of recovery in myositis the distinction is obviously of the greatest importance, but may present peculiar difficulty. In any case of apparent muscular dystrophy, not obviously genetically determined, a thorough search should be made for evidence of inflammation or of skin involvement in the past. Clinical features in favour of myositis are weakness of the neck muscles, which is rare in dystrophy apart from the myotonic form, dysphagia or ptosis and ocular

weakness. The initial complaint is often of easy fatigue rather than constant weakness and, as is mentioned below, a response to neostigmine may be obtained. The diagnosis may remain in doubt after the most careful consideration and muscle biopsy is performed in most cases.

Muscle biopsy

A muscle that is definitely but not severely affected should be chosen, as a completely atrophied muscle seldom shows any diagnostic features. A cylindrical strip some 0 5×2 centimetres should be obtained with as little manipulation as possible, and sections should be cut in both transverse and longitudinal planes

The interpretation is notoriously difficult. After a carefully planned investigation covering a wide field of muscular disease Greenfield and his colleagues (1957) reached the depressing conclusion that "No single change has been found specific for any disease, and even combinations of changes are no more than highly suggestive". While admitting the difficulties, Walton and Adams (1958) concluded that the distinction between dystrophy and myositis "can often be made with certainty on the basis of the pathological features". Typically, myositis shows variation in fibre size, degeneration and necrosis, infiltration with inflammatory cells and changes thought to be those of regeneration of muscle fibres These changes can be unmistakable but, in the present author's experience, usually when the clinical diagnosis is in little doubt. In many cases the biopsy is inconclusive and, on occasion, may be perfectly normal. This may be owing to patchy distribution of the lesions in any individual muscle and a normal biopsy from an obviously weakened muscle is even of some diagnostic value as it is not likely to occur in a case of dystrophy. It must be confessed that the routine muscle biopsy is often disappointing and it is to be hoped that the method of biopsy after intravital staining with methylene blue, developed by Coërs (1955), will eventually provide more precise information. This method is already revealing a wealth of new information about the terminal nerve supply of skeletal muscle but the clinical associations of these hitherto entirely unfamiliar appearances are not yet fully understood.

Electromyography

The electromyographic changes in polymyositis as distinct from muscular dystrophy are still a matter for argument among experts Electromyography is an extremely useful method of detecting muscle disease and of distinguishing myopathic from neuropathic lesions, but few would now claim to be able to distinguish with certainty features characteristic of any specific disease of muscle. In both myositis and dystrophy the record shows distortion and reduction of amplitude of motor unit potentials on voluntary contraction, as opposed to the gross reduction in the number of action potentials in neurogenic atrophy.

Association with malignant disease

Dermatomyositis has long been known to occur in association with malignant disease and clinically very similar muscular weakness is now known to occur without skin lesions. Some controversy exists as to whether these cases are polymyositis or a distinct entity "carcinomatous myopathy". Clinically, the cases are

not to be distinguished from polymyositis but the muscles are stated not to show any evidence of this disease, even at post mortem examination (Brain and Henson, 1958) The answer cannot at present be given but it is of some practical importance that progressive or even remittent weakness of the limbs may be evidence of occult malignant disease, most commonly of the lung.

Prognosis and treatment

Prognosis in polymyositis is a matter of grave difficulty and only rather vague generalizations can be given. According to Walton and Adams (1958) the prognosis is better when the pathological process is almost or completely confined to the muscles. Of such patients about half may be expected to show marked improvement or complete remission, but the detection of these fortunate cases is not possible at the height of the illness. Remarkably enough even carcinomatous myopathy may improve or recover completely even when the associated growth is rapidly progressing. This incalculable natural history makes the assessment of treatment very difficult, but there is agreement that some cases improve on treatment with corticotrophin or cortisone and that no other treatment is of proved value It is again impossible to predict response to treatment and every case, not already improving, should be treated.

AMYOTONIA CONGENITA

The clinical problem presented by the weak and hypotonic infant is one of great difficulty. This syndrome may be a symptom of many diseases not directly related to muscle When these can be excluded there remains a group of cases to which the label of amyotonia congenita is frequently attached. This disease, as originally described by Oppenheim (1900), had a relatively good prognosis and a definite tendency to improvement. This fortunate outcome is comparatively rare in hypotonic infants and the death rate is high owing to the relative frequency of the progressive spinal atrophy of Werdnig and Hoffman. Considerable doubt arose as to the existence of a separate group of different aetiology and better prognosis, but Oppenheim's findings have recently been confirmed by Walton (1956a) who reported that 17 out of 109 cases previously diagnosed as amyotonia congenita were of this type Not all recovered completely, showing some residual weakness, but clearly the outcome is quite different from the inexorable advance of spinal atrophy. Walton suggested that these cases should be called "benign congenital hypotonia", but there seems little reason to abandon the euphonious amyotonia congenita. It is true that cases are frequently erroneously placed in this category, but this mistake can usually be avoided. Clinical examination in spinal atrophy frequently shows fibrillation of the tongue and grave respiratory weakness. These signs are not always present at a single examination and, if it is essential that the prognosis be known at once, a muscle biopsy will be conclusive. In amyotonia congenita the muscle will appear normal while in spinal atrophy there will be definite evidence of neurogenic atrophy.

MYASTHENIA GRAVIS

Advances in understanding myasthenia gravis have been accompanied by increasing

difficulty in defining the condition. The cardinal features of easy fatigability reversed by neostigmine are undoubtedly present in some cases of polymyositis (Walton and Adams, 1958) and carcinomatous myopathy (Brain and Henson, 1958) Myasthenia is probably better regarded as a symptom, but the mechanism of its production and the causal connexion of such clinical correlations as have been observed remain very obscure. The central problem in classical myasthenia gravis is to explain fatigability and weakness occurring selectively, often undergoing a natural remission, and reversible by the action of anticholinesterases. It is now known that clinically unaffected muscles in a myasthenic, and even the muscles of a myasthenic in remission, are, nevertheless, abnormal. Churchill-Davidson and Richardson (1952) showed that such muscles react abnormally to decamethonium iodide and that clinically affected muscles are only quantitively different from the apparently unaffected muscles in the same patient. This demonstration of a generalized and persistent abnormality is important as it is at least compatible with the idea of a humoral agent responsible for the neuro-muscular block. *Without entering into the intricacies of neuro-muscular transmission and block* it now seems probable that acetylcholine is produced in normal quantities at the myo-neural junction but that it is prevented from acting normally on the motor end-plate (Churchill-Davidson, 1956). Anticholinesterases permit the accumulation of acetylcholine so that the defect can be overcome. The nature of the process preventing normal access or action of acetylcholine is unknown. Coers and Desmedt (1958) have reported consistent and specific anatomical changes in the motor end-plates, as visualized by intravital staining. The significance of this finding is not yet clear and any theory based on such anatomical findings must take into account the fact that complete and prolonged clinical remission not infrequently occurs.

Little has been added to the classical clinical descriptions *Wasting and* irreversible weakness are now recognized as occurring more frequently than was formerly believed (Rowland and Eskenazi, 1956). An advance in diagnosis has been the introduction of edrophonium chloride (Tensilon), a very short acting anticholinesterase. An intravenous injection of 10 milligrams will produce dramatic but very brief improvement and as a diagnostic test has great advantages over neostigmine.

Treatment

Neostigmine is [illegible] dostigmine bromide *(Mestinon)* has c [illegible] with generalized [illegible] neostigmine as a [illegible] ments vary greatly and the medical treatment of myasthenia may require considerable judgment It must be recognized that the weakness, particularly of ocular muscles, is not always fully reversible, however high the dose of anticholinesterase, and that overdosage with these drugs may itself produce severe weakness. This may be distinguished from residual myasthenic weakness by the injection of Tensilon which will not, of course, reverse the weakness of anticholinesterase overdosage. The treatment of acute severe paralysis in a myasthenic, the myasthenic

crisis, should always begin by ensuring that it has not been caused by overdosage. The crisis, with respiratory muscle weakness, is an extreme emergency. Rowland and his colleagues (1956) have emphasized that fleeting attacks of respiratory distress should be taken as a warning of an impending crisis, that sedatives should be used with great caution and that mechanical respiration should be used early.

Thymectomy

Despite advances in medical treatment myasthenia is often a disabling and dangerous disease which may become temporarily or permanently resistant to usually effective drugs. It is natural, therefore, that any alternative and curative method of treatment would be welcome and thymectomy has been extensively practised in the last 10 years The frequency with which thymomas are associated with myasthenia forms the only rational basis for this treatment and it does not at present appear probable that the thymus in myasthenia secretes a neuro-muscular blocking agent in sufficient quantity to produce the symptoms of the disease. In the absence of knowledge it is unprofitable to argue on theoretical grounds and assessment must be entirely on the results. It is at once clear that thymectomy is in no way comparable to thyroidectomy for hyperthyroidism, where the results are predictable within narrow limits, and it is not infrequent for thymectomy to have no influence at all in a case of myasthenia. Statistical comparison of operated and unoperated cases, after exclusion of thymomas, appears to favour operation, especially in lowering the mortality in young women (Simpson, 1958). There are many mild cases with weakness almost confined to ocular muscles where thymectomy should never be considered, but most authorities would probably agree that in a young patient with generalized myasthenia who had shown no signs of a natural remission within 2 years, thymectomy should be advised According to Keynes (1954), the great proponent of thymectomy in Great Britain, the operation is contra-indicated in thymomas, at least until after x-ray therapy There can be no place for the occasional thymectomist Selection of cases and pre-operative and post-operative care are highly specialized, and experience is likely to be acquired dearly

CONCLUSION

In this brief and partial review only the more important recent advances have been outlined. Modern concepts of primary muscle disease may well appear more [illegible]

of disease of muscle progresses beyond the stage of clinical description alone.

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Mortality rates

From analysis of the reported cancer deaths in the United States for 1948, Steiner (1952) found that primary bone cancer represented about 1 per cent of all fatal malignant tumours: his figures include, of course, any metastatic bone tumours misdiagnosed as primary. In Great Britain, about the same relative incidence of primary bone cancer is obtained from mortality figures, the returns of the Registrar General for 1950–1954 (McKenzie, 1957) giving an incidence of 0·8–0·9 per cent of all malignant tumours. The same source gives annual death rates of 14·4 (for males) and 9·5 (for females) for primary bone cancer, expressed per million of living population of England and Wales, about 500–600 deaths per year being ascribed to this cause. (Steiner's American figures correspond to a death rate of approximately 15 per million.) Thus it can be seen that primary bone cancer is a relatively rare condition.

Age incidence

The figures for the incidence of malignant bone tumours become of greater interest when they are shown in relation to age. Fig. 42 shows that mortality is low under the age of 5 years and rises to a first peak between 15 and 20 years. A second rise commences after the thirtieth year and continues until the age-group 75–79 years. One would like, of course, to have similar information for each type of malignant bone tumour, and one would expect the shape of the curves to differ widely. In the absence of such information, it is of interest that the incidence of

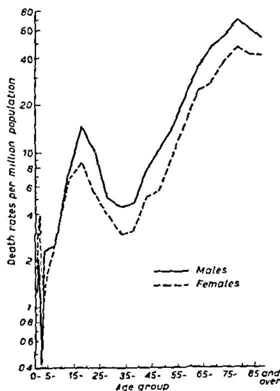


FIG. 42.—Malignant bone tumours: death rates per million living, by sex and age, 1950–1956, England and Wales (From the *Registrar General's Statistical Review for 1956*, by courtesy of The Controller, H.M. Stationery Office).

osteogenic sarcomas in the area of south-west England covered by the Bristol Bone Tumour Register (Price, 1955) shows the same type of bimodal curve.

Geographic and racial distribution

Although it is well known that the incidence of many types of cancer varies in different countries and in different racial groups, there is so far little information available regarding the geographic or racial distribution of bone tumours. Although it is not, strictly speaking, a bone tumour, adamantinoma of the jaw has been noted by Steiner (1954), in a recent survey of racial and geographic aspects of cancer, as a tumour which shows an unusually high incidence in Chinese and Negroid races More recently, a remarkable preponderance of jaw tumours has been reported by Davies (1959) in a survey of cancer in Africans. Of 120 bone tumours observed, 86 were situated in the jaws. The jaw tumours were adamantinomas in adults; in children they took the form of unusual multifocal sarcomas involving the mandible or the maxilla or both these bones, and apparently arising in the region of the dental laminae of the developing molar teeth.

CLASSIFICATION

It must be stressed that tumours of bone make up an extremely varied group of lesions The aim of classification is, of course, to group like with like, and, from a knowledge of the properties of the various groups, to predict the clinical behaviour of a particular lesion

Ideas on the relationships of the various types of malignant tumours have developed steadily since the establishment of the Bone Sarcoma Registry of the American College of Surgeons in 1921. At that time it was widely felt that a number of different varieties of malignant bone tumour existed, that these might be recognized by a study of their histological characteristics, and that the ultimate justification of a histological system of classification and nomenclature must be the demonstration of prognostic differences between the various types of tumour listed In more recent years, knowledge of the previously uncharted field of benign tumours of bone has been clarified by the recognition of a number of definite entities, such as osteoid osteoma, benign osteoblastoma, chondromyxoid fibroma, non-osteogenic fibroma, and benign chondroblastoma, chiefly due to the work of Jaffe and Lichtenstein (Jaffe, 1958) Not only did the recognition of these entities demonstrate the effectiveness of the histological diagnosis of bone tumours, but it helped the analysis of the previously confused malignant groups by removing from them lesions which had been included in error.

In addition to the above benign tumours, a number of new entities have been recognized among malignant bone tumours, but with these the tendency has been, on the whole, towards simpler classification through the avoidance of unjustified subdivision Table I lists various types of primary bone tumour (based on the work of a number of authors, including Jaffe, 1958, Lichtenstein, 1951, 1952, Sissons, 1958; and Thomson and Turner-Warwick, 1955) which are probably generally acceptable today.

Criteria for classification

Classification and nomenclature of tumours of bone, as with other types of

TABLE I

TYPES OF PRIMARY BONE TUMOURS

Taking origin from "skeletal connective tissue"

Malignant tumours	*Benign tumours*
Osteosarcoma	Osteoid osteoma
(1) ordinary type	Benign osteoblastoma
(2) slowly growing parosteal osteosarcoma	Enchondroma (solitary or multiple)
Chondrosarcoma	Cartilage capped exostosis (solitary or multiple)
(1) primary	Benign chondroblastoma
(2) secondary	Chondromyxoid fibroma
Fibrosarcoma	Non-osteogenic fibroma
Giant cell tumour	

Taking origin from other skeletal components

Malignant tumours	*Benign tumours*
"Adamantinoma"	Lipoma
Chordoma	Angioma
Lymphoid and haemopoietic neoplasms	Neurilemmoma and neurofibroma
(1) Reticulosarcoma	
(2) Lymphosarcoma	
(3) Hodgkin's disease	
(4) Leukaemias	
(5) Myelomatosis	
"Ewing's tumour"	
Angiosarcoma	
Liposarcoma	

neoplasm (Willis, 1953) should incorporate information on the following items: (1) Tissue of origin, (2) type and degree of differentiation shown by tumour tissue; (3) behaviour—either observed or expected.

Classification is based on histological structure and makes use of a histological nomenclature, although clinical and radiological information is also important in the identification of an individual lesion and in the characterization of a particular tumour type.

It is to be noted that the histological structure of a tumour, that is, the particular type of structural differentiation present, is not always an exact guide to its origin. One might be inclined to infer, for example, in the case of a malignant tumour which showed osteoblastic differentiation, that is, an "osteosarcoma", that the tumour took its origin from preformed osteoblasts, and this might appear to be confirmed by the fact that the majority of such tumours occurred in the skeleton. But the error is revealed by their less frequent occurrence in soft tissues, and we can only infer that the tumour is of connective tissue origin. This, in fact, is the position with most bone tumours: with few exceptions, we are unable to make direct observations on the tissue from which they take origin, and we can only say that "skeletal connective tissue"—that family of diverse but probably interrelated cells which cover the surfaces of bony structures and occupy the lacunae in the tissue matrix—is concerned. Infrequently, as with "secondary" chondrosarcoma, we are able to observe the origin of a tumour from a specific type of skeletal tissue (in this case, pre-existing cartilage), while with chordoma, the fact that this type of tumour occurs only in the axial skeleton, together with the

particular pattern of differentiation it shows, strongly suggests an origin from remnants of notochordal tissue Similar considerations suggest that vascular, lymphoid, and haemopoietic neoplasms take origin from skeletal components other than "skeletal connective tissue" (Table II).

TABLE II

TISSUE OF ORIGIN FOR VARIOUS SKELETAL TUMOURS

Type of tumour	*Tissue of origin*
Metastatic carcinoma	Extraskeletal epithelial tissue
Adamantinoma of jaw	Residues of dental epithelium
"Adamantinoma" of tibia	?
Chordoma	Notochordal remnants
Angioma, and other primarily vascular tumours	Blood vessels of bone
Lymphoid and haemopoietic neoplasms of [illegible]	Bone marrow
[illegible]	?
[illegible]	Pre-existing cartilaginous lesions, such as exostoses and enchondromas
Most benign tumours of bone	"Skeletal connective tissue"
Most malignant tumours of bone	"Skeletal connective tissue"

Differentiation, then, is a description of what the tumour cells are doing, and not a specific indication of the type of cell from which the tumour has had origin. If most of the primary tumours of bone, as outlined above, take origin from the same tissue, they certainly differ with regard to the type and degree of differentiation they show: indeed it is from a study of these factors that the histological diagnosis is made. Certain tumours, for instance, show osteoblastic differentiation, their cells possessing a general similarity to non-neoplastic osteoblasts Some of these, belonging to the "benign osteoblastoma" or "osteoid osteoma" groups, show the uniformly high degree of structural differentiation characteristic of a benign tumour· others show instead the general features of a malignant tumour with some less differentiated highly cellular or even pleomorphic areas, and are known as osteosarcomas. Each histological tumour type, in fact, represents a particular type or pattern of structural differentiation. with the malignant tumours related to skeletal connective tissue there appear to be four main varieties of these, each corresponding to one of the cell types normally encountered in the skeleton (see Table III)

With some of the benign tumours, such as chondroma or benign osteoblastoma, the correspondence of the type of differentiation to a normal cell type (cartilage cell, or osteoblast) is equally clear with others, such as benign chondroblastoma and chondromyxoid fibroma, although the patterns of differentiation are distinctive, we do not yet fully understand their relationship to normal cell types.

[illegible]
cla [illegible]
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such as age and sex incidence, anatomical distribution, and—in particular—their

TABLE III

MALIGNANT TUMOURS OF SKELETAL CONNECTIVE TISSUE

Type of tumour	*Corresponding normal cell type*
Osteosarcoma	Osteoblast
Chondrosarcoma	Cartilage cell
Fibrosarcoma	Fibroblast
Giant-cell tumour (osteoclastoma)	*Osteoclast*

biological behaviour. Its uniformly good prognosis, for instance, is the ultimate justification for separating benign chondroblastoma from the more malignant giant-cell tumour, although differences of anatomical distribution, and of age and sex incidence also contribute to the distinction between the two lesions (*see* Sissons, 1956) Similarly, there appear to be important differences in the degrees of malignancy of the four main categories of malignant bone tumour (*see* Coley, 1949; MacDonald and Budd, 1943; O'Neal and Ackerman, 1952; Thomson and Turner-Warwick, 1955) although few comparative studies have yet been based on accurate histological diagnosis.

At the present stage of knowledge, we are on the safest ground if we regard any scheme of classification of bone tumours as a practical instrument without too many theoretical implications concerning the relationships between the various groups. the subdivisions shown must ultimately be justified by the distinctness, from the clinico-pathological viewpoint, of the various "entities" listed.

Specificity of histological differentiation

At this point we should consider the extent to which the various types of bone tumour, each recognized by the possession of a particular type of histological differentiation, are to be distinguished from one another. Here, we must recall that a tumour does not show the same histological appearance in all areas: the evidence of differentiation on which identification depends may be present in only a few areas, and it is well known that tumours of widely different types may present undifferentiated areas which are indistinguishable from one another. A more interesting problem is presented by those tumours which show evidence of more than one type of differentiation. From the theoretical point of view, several authors (Johnson 1953; Willis, 1953) have emphasized this as a feature of skeletal

had origin, but it should be stressed that it is not sufficiently frequent or [illegible] to be a bar to practical diagnosis. When it is encountered, it necessitates certain arbitrary decisions on the affinities of the tumour, and these will ultimately be decided by the further study of the cases concerned and of others like them It is here, in particular, that agreement on histological grouping has not yet been achieved by different authorities, and that precise criteria for classification have

still to be laid down. Occasionally, a problem of this type is occasioned by the presence of both bony and cartilaginous differentiation in the same malignant tumour. The usual definition of chondrosarcoma (Sissons, 1958) as a purely cartilaginous tumour excludes this type of lesion, which is accordingly grouped with osteosarcoma. The amount of cartilage is usually small, but is sometimes large enough to be confusing. Only further work, correlating the results of careful histological study with clinical data and follow-up information will show whether the current grouping of lesions of this type is correct, whether they should be regarded as chondrosarcomas, or whether they make up a separate group Similar problems are occasionally met with in connexion with the distinction between osteosarcoma and the more malignant types of giant-cell tumour, and less frequently with other types of lesion. Another problem of practical classification, related to specificity of histological differentiation, is occasioned by the rare completely undifferentiated malignant tumour, which evades all attempts to allocate it to any of the usual groups.

Behaviour

The degree of histological differentiation usually has an important bearing on the behaviour of a tumour· in general benign tumours are highly differentiated and malignant tumours are poorly differentiated or "anaplastic". But it has become evident that for some types of tumour, "benign" and "malignant" are relative terms (Willis, 1953), and one consequence of this is the recent tendency to extend classification based on behaviour within any particular group by the recognition of a number of "grades" of malignancy. Thus it is current practice in some centres to use numerical grading systems in order to aid the prediction of clinical behaviour of chondrosarcomas (O'Neal and Ackerman, 1952), giant-cell tumours (Jaffe, Lichtenstein and Portis, 1940) and even osteosarcomas (Price, 1956) Such prediction is, of course, most desirable, but the apparent precision of numerical grading can sometimes be misleading Variations in histological appearances in different parts of a tumour certainly limit the value of any assessment that is made on a small biopsy sample, and in any case further work is necessary in order to determine the histological criteria for the various grades and to judge the effectiveness of the prediction achieved

TABLE IV

DISTRIBUTION OF TUMOUR TYPES

Malignant tumours		Benign tumours	
Osteosarcoma (ordinary type)	469	Cartilage-capped exostosis	272
Osteosarcoma (parosteal type)	21	Enchondroma	99
Chondrosarcoma	218	Osteoid osteoma and benign osteoblastoma	74
Fibrosarcoma	58	Benign chondroblastoma	17
Giant-cell tumour	120	Chondromyxoid fibroma	13
Ewing's tumour	141	Other benign tumours	53
Reticulum-cell sarcoma	70		
Myelomatosis	563		
Chordoma	80		
Other malignant tumours	8		
Total malignant tumours	1,748	Total benign tumours	528

Relative frequency of various types of bone tumour

Some idea of the relative frequencies of the different types of bone tumour, benign and malignant, can be obtained from a survey (Dahlin, 1957) of the 2,276 cases of primary bone tumour diagnosed at the Mayo Clinic between 1909 and 1955. In this material, the distribution of tumour types is as shown in Table IV.

AETIOLOGY

The nature and cause of neoplastic change is, of course, a wide and active field of biological research at present. There is an almost complete lack of any direct information regarding the causation of human bone cancer, and—apart from the field of radiation carcinogenesis—relatively little work on the mechanism of production of bone tumours under experimental conditions in laboratory animals, but the various possibilities for bone carcinogenesis are indicated by the trend of cancer research as a whole. The basic change in tumour formation has come to be regarded by many authorities (*see*, for instance, Burnet, 1957) as a change in the character of the constituent cells which makes them insusceptible to normal control. This may result from the action of a number of different agents, including a wide range of chemical compounds such as carcinogenic hydrocarbons and certain hormones, physical agents such as ionizing radiations, and biological agents such as the viral causes of a number of animal tumours, for example, Rous chicken sarcoma, Shope papilloma and Bittner milk factor. The actual conversion from a normal to a malignant cell, whatever its cause, has become increasingly regarded as genetic in nature, and probably consists of a series of somatic mutations associated with increasing growth potential. Such a sequence of events was originally suggested by Muller (1951), and has received general confirmation from studies of the incidence of a number of different types of human cancer in various age-groups, the type of increasing incidence with increasing age observed by Nordling (1953) and by Armitage and Doll (1954) suggesting a series of about 6 such mutations. This interesting field has recently been reviewed by Koller (1957).

In man, the particular pattern of age incidence observed for malignant bone tumours, and illustrated in Fig 42, suggests that a number of aetiological factors are at work, and that they are not the same in childhood as in adult life. Most other types of malignant tumour show a steadily increasing incidence with increasing age, and as already noted, this is believed to be consistent with the idea of a series of somatic mutations, sometimes thought to result—at least in part —from exposure to environmental carcinogenic agents. Certain tumours of childhood, such as acute leukaemias, Wilms' tumour, and a variety of endocrine tumours, show a very different age-mortality curve (Registrar General, 1958). There is appreciable mortality during each of the first 5 years of life, and this drops rapidly during the second quinquennium It would appear that these types of tumour result from some inherent abnormality of development and early growth. With malignant bone tumours, however, the position is again different (*see* Fig 42), the increasing mortality during the entire childhood period suggesting to some authors (Price, 1958; Duthie, 1959) that the neoplastic process represents an

abnormality—possibly hormone dependent—of a later period of growth. One factor contributing to (but not by itself responsible for) the increasing incidence of malignant bone tumours in later life is Paget's disease of bone While present in about 3–4 per cent of the population above 40 years of age (Collins, 1956), this condition is present in about 30 per cent of patients with malignant bone tumour over the age of 50 years (Coley and Sharp, 1931; Gerstel and Janker, 1933; Thomson and Turner-Warwick, 1955). Multiple malignant bone tumours have not infrequently been reported in Paget's disease (*see* Sissons, 1958)

Genetic factors

The ultimate importance of genetic factors in influencing the development of bone tumours is evident in the widely differing incidence of these lesions in different animal species, and in different strains within the same species. Spontaneous bone tumours appear to be relatively common in man and in the dog, less so in rats and mice, and virtually unknown in the rabbit. By selective breeding, a number of workers have developed strains of mice showing an unusually high incidence of primary bone tumours. Such a strain was described by Pybus and Miller (1938a), and showed a greater incidence of bone tumours in females than in males (Pybus and Miller, 1938b). Some of the tumours were clearly malignant, having the histological appearance of osteosarcoma, chondrosarcoma, or spindle-celled sarcoma, and producing pulmonary metastases which were sometimes bone forming (Pybus and Miller, 1940a and b)

A genetic abnormality in man, which—admittedly in very few cases—is concerned with the development of malignant bone tumours, is hereditary multiple exostoses. This condition, sometimes known as diaphysial aclasis, is the result of a Mendelian dominant mutant gene, and is occasionally complicated by the development of malignancy. Reported series of cases vary in the incidence of such change, but in one series it was present in as many as 10 per cent of cases studied (Jaffe, 1943) Apart from isolated and unusual cases of this sort, however, the general role of genetic factors in determining the development of "spontaneous" bone tumours still requires to be elucidated by means of such techniques as studies of familial or sibling incidence, twin studies and assessment of the incidence of bone tumours in racial or other groups of different genetic constitution.

The direct role of a genetic, that is, a mutational, change in the production of malignant change, as opposed to the influence of genetic factors on the frequency of occurrence of malignant change, was referred to above where it was noted that such a process of somatic mutation was possibly the basis of all malignant change. It has not been directly observed with bone tissue, but it is clearly the explanation of the sudden occurrence of malignancy in serially transplanted, but otherwise untreated, tissue cultures of mouse fibroblasts, as reported by Sandford, Likely and Earle (1954) The presence of malignancy was established by the development of fibrosarcomas when the cultures were injected into mice belonging to the same strain from which they had been obtained.

Virus infection

A number of different types of tumour in animals (including the Rous chicken sarcoma, avian leucosis, the Shope rabbit papilloma, certain breast tumours in

mice, and mouse leukaemia) have been shown to result from infection with viruses. At present, there is considerable interest in the chemical and immunological inter-relations between such "extrachromosomal" factors and the genetic material of the nucleus, but there is little or no evidence to support the view that ordinary types of human cancer are of viral origin. Work on viral carcinogenesis has recently been reviewed by Dmochowski (1957).

That the skeleton can be affected by some of the avian viral agents is apparent from the bone changes (usually regarded as non-neoplastic) present in avian leucosis (Burmester, 1947), and from the findings of Berg (1932), who showed that bone sarcomas could develop when an avian sarcoma virus was introduced directly into bone tissue. Stewart (1955) has produced a variety of tumours in C_3H mice by a filterable agent obtained from mouse leukaemia. This agent could be passaged serially in tissue culture, and was highly antigenic. Recently, Stewart, Eddy and Stanton (1958), using the same filterable agent, have reported the experimental production of osteosarcomas in rabbits, mice, rats and hamsters. The cancerous nature of such virus-induced lesions is, however, not accepted by all workers (Goodpasture, 1957).

Hormones

The action of hormones in influencing the formation and subsequent behaviour of a number of types of tumour, both in experimental animals and in man has been amply established (*see* Bielschowsky and Horning, 1958, for a review of hormone carcinogenesis). Pituitary, gonadal and adrenocortical hormones are of particular interest in this connexion, and "hormone-dependent" tumours include certain breast and prostatic carcinomas where either hormone treatment or surgical removal of endocrine tissue plays an important part in the clinical management of cases.

Bone tissue is influenced by a variety of hormones, including pituitary growth hormone, thyroid hormone, insulin, parathyroid hormone, adrenocortical and gonadal hormones (*see* Bourne, 1956, for useful reviews), the growth and maturation of the developing skeleton, and the metabolic turnover of the adult tissue being greatly affected by these agents. Despite this relationship, however, any link between hormonal control of the skeleton and tumour formation is purely a matter of conjecture.

The relationship between oestrogens and bone is of considerable interest. Observations on the egg-laying cycle in birds (Bloom, Bloom and McLean, 1941; Kyes and Potter, 1934) showed the remarkable development and resorption of a mass of spongy bone in the marrow cavities of long bones, and led to the investigation of the effects of oestrogens on the bones of a variety of species. Wentworth, Smith and Gardner (1940) showed an increase in the mineral content of the bones of mice following oestrogen treatment. The histological aspects of the medullary bone formation concerned, and in particular the interference with normal metaphysial remodelling, have been described by many authors including Day and Follis (1941) and Budy, Urist and McLean (1952).

In view of the difference in sex incidence in the inbred "bone tumour strain" of Pybus and Miller (1940a and b), Miller, Orr and Pybus (1943) investigated

the effects of oestrogen administration on this strain of mouse. They found a rather unusual skeletal reaction, consisting of new bone formation together with intense osteoclasis, but they were not able to demonstrate any alteration in tumour incidence in their oestrogen-treated animals.

In man, differences of sex-incidence for certain types of bone tumours, and the occurrence of a considerable number of malignant tumours during the period of active skeletal growth and maturation (Fig. 42) indicate at least the possibility of some hormonal influence on tumour formation, but more evidence is still needed on this subject.

Chemical carcinogenesis

In experimental animals, bone tumours have been produced with a variety of carcinogenic materials, including otherwise inert metals (Schinz, 1942), but there is no reason to believe that these substances play any part in the development of "spontaneous" human tumours. Brunschwig (1938) observed tumours, which he described as fibrosarcomas, in 4 of 33 rats 8–12 months after paraffin pellets containing methylcholanthrene had been inserted into the marrow cavity of the femur or tibia. Brunschwig and Bissell (1938) observed 2 tumours after similar insertion of cholesterol pellets containing benzpyrene in 29 rats and mice. They described one of these as a fibrosarcoma and the other as an osteosarcoma, but it is not clearly established that the latter tumour was bone-forming. Sissons (1950) reported a large series of bone tumours induced in rats and mice with methylcholanthrene, 9:10 dimethyl-1:2-benzanthracene or benzpyrene. On histological examination they were all anaplastic spindle-celled or round-celled tumours, and they failed to show any specifically bony or cartilaginous differentiation. It would consequently appear that tumours induced with carcinogenic hydrocarbons in small rodents do not have any special bone-forming properties that distinguish them from tumours arising in soft tissues.

Petrov and his colleagues (1952) observed one malignant osteolytic tumour in a rhesus monkey about 3 years after the insertion of a paraffin pellet containing 30 milligrams of methylcholanthrene into the marrow of the tibia. The limb was amputated, and the tumour described as a "polymorphic sarcoma of the osteogenic type", but no information regarding any specific bony or cartilaginous differentiation was given. The monkey was alive 2½ years after the amputation. Eleven other monkeys had received varying amounts of either 9:10 dimethyl 1:2-benzanthracene or methylcholanthrene, but had not developed tumours at the time of the report.

Of great interest are the bone tumours which have been induced in the rabbit by the administration of certain poorly-soluble beryllium compounds, usually by intravenous injection (Barnes, Denz and Sissons, 1950; Dutra and Largent, 1950; Gardner and Heslington, 1946, Janes, Higgins and Herrick, 1954). It is clear from these accounts that beryllium-induced sarcomas in rabbits are malignant lesions which metastasize by the blood-stream to the lungs and other organs. They are frequently multiple, and they show something of the structural variation encountered in human malignant bone tumours, conspicuous tumour bone formation and cartilaginous differentiation being present. This type of tumour might well provide a convenient experimental counterpart to human bone tumours,

and they have provided interesting information regarding the histogenesis of bone tumours and their relationship to precancerous change.

Radiation carcinogenesis

A considerable amount of experimental work, as well as some human experience, has shown that bone tumours are readily produced by ionizing radiations, both from external sources and from internally deposited radioactive materials The fact that bone is a calcified tissue contributes materially to this in two ways. In the first place, with certain external radiations it results in a build up of local secondary ionization in the tissue, with the result that cells on bone surfaces and in small cavities receive substantially higher doses than the surrounding soft tissues (Spiers, 1950, 1951). Secondly, a number of radioactive materials such as radium, ^{90}Sr, ^{32}P, ^{91}Y, because of their chemical nature, are selectively deposited, after injection or ingestion into the body, in the calcified material of the skeleton *and teeth, and are retained there for long periods. Their patchy distribution in the* skeleton results in certain areas of bone tissue being subjected to relatively high localized doses of irradiation.

External irradiation

Abundant clinical evidence testifies to the occasional production of bone tumours by external irradiation with x-rays or *gamma*-rays A number of cases showing tumour development following therapeutic irradiation were collected by Hatcher (1945), and the subject has been reviewed by Cahan and his colleagues (1948) In all about 39 cases have been reported, the latent period varying from 5 to 20 years. It is probable that in a number of cases the connexion between irradiation and tumour formation is not realized either by the patient or his physicians because of the length of the intervening period. While it appears that a tissue dose of about 3,000 roentgens is usually required for the induction of malignant change, in one of the reported cases a sarcoma was produced by a *dose of 1,550 roentgens. The incidence of tumours in patients receiving doses of* this order must be very small, but the hazard should weigh against the use of irradiation for the treatment of benign lesions of bone, particularly in young patients, until more is known of the relationship between dose and tumour induction.

Little work appears to have been done experimentally in connexion with the production of bone tumours by external irradiation Ludin (1934) and Ross (1936) have reported osteosarcomas after local irradiation; Lacassagne and Nyka (1937) have reported osteosarcomas *of the sella turcica in rabbits after* the introduction of radon tubes into the pituitary. Koletsky and Gustafson (1955) observed osteogenic sarcomas in 5 of 123 rats which survived 6 months or longer after being given whole body irradiation of 660 roentgens.

Bone tumour formation, of course, is not the only hazard of *skeletal irradiation*. [illegible] infection

[illegible]

but more widely distributed doses, evidence of an excessive incidence [illegible]

has been obtained This first became apparent through a study of mortality in American radiologists, who may well have received appreciable doses of irradiation in the course of their occupation (March, 1950), and has been confirmed by experience with the irradiated survivors of Hiroshima and Nagasaki (Lange, Moloney and Yamawaki, 1954) and patients treated by radiotherapy for ankylosing spondylitis (Court-Brown and Abbatt, 1955).

Internal irradiation

Here the initial observations were the studies of Martland (Martland, 1931; Martland and Humphries, 1929) on bone tumour development in workers using luminous paint in the manufacture of watch dials. Minute quantities of radium and mesothorium were ingested in the process of "pointing" the brushes between the lips, and these materials became localized in bone tissue. Patchy necrosis was followed by irregular bone resorption; if the patient survived the anaemia which sometimes was produced by damage to the haemopoietic marrow, bone tumours frequently developed. The tumours were osteosarcomas, and were sometimes multiple The development of bone sarcomas has since been observed in other groups of individuals ingesting radium, this sometimes having been administered for therapeutic purposes (Aub and his colleagues, 1952; Looney, 1956; Looney and his colleagues, 1955; Looney and Woodruff, 1953).

Experimentally, similar tumours have been produced in a wide range of animal species following the administration of either radium (Dunlap and his colleagues, 1944, Hellner, 1937; Petrov and his colleagues, 1952, Sabin, Doan and Forkner, 1932; Schürch and Uehlinger, 1935) or a variety of "bone-seeking" radioactive isotopes such as ^{89}Sr, ^{90}Sr, ^{239}Pu and ^{45}Ca (Anderson, Zander and Kuzma, 1956; Brues, Lisco and Finkel, 1946, Cherkasskii, 1956; Heller, 1946; Koletsky, Bonte and Friedell, 1950; Kuzma and Zander, 1957a; Litvinov, 1956 a and b, Owen, Sissons and Vaughan, 1957, 1959; Skoryna and Kahn, 1959). Tumours occur at the sites of maximum isotope deposition and retention (Owen, Sissons and Vaughan, 1957) which are determined by the activities of bone growth and remodelling processes in different parts of the skeleton. In rabbits (Owen, Sissons and Vaughan, 1957, 1959) tumours occurred most frequently in the metaphyseal regions of the long bones (in young growing animals) and in the region of growing teeth: isotope deposition and retention is high in each of these situations.

Finkel (1958) discussed the incidence of bone tumours in mice receiving small doses of ^{90}Sr, and considered the extrapolation to man of these results in connexion with present body burdens of ^{90}Sr due to atomic fall-out. The results concerned can be interpreted as consistent with a threshold value for tumour induction which is well above currently envisaged human bone levels But it must be noted that not all authorities accept the idea of such a threshold, particularly with regard to the genetic—as opposed to the pathological—effects of irradiation. This uncertainty with regard to the existence of a threshold for radiation-induced damage to biological material makes it impossible for us to decide whether natural background radiation (such as that due to cosmic rays, naturally occurring radium and now to atomic fall-out) plays any part in the causation of "spontaneous" bone tumours or other types of malignant disease. Available information is veiled in

statistical uncertainty, but data on the incidence of bone tumours in human populations with different body burdens of natural radium—due chiefly to variation in the radium content of water supplies—may well provide information "which may have its bearing on the likely effect of low concentrations of other types of radioactive material in the human skeleton" (Marinelli, 1958).

TISSUE CULTURE AND TRANSPLANTATION

The techniques of tissue culture and transplantation have been applied to many types of tumour, and have provided important information on the behaviour of the tumour cells when separated from their normal surroundings. A tumour growing under the more standardized conditions of tissue culture or successful serial transplantation provides a very convenient system for the investigation of the effects of chemotherapeutic substances, and many anti-cancer agents are being tested in this way. It must, however, be remembered that information obtained from such experimental work may not be directly applicable to the tumour in its normal habitat, because of the different environment and conditions of growth.

Little work appears to have been carried out on the tissue culture of bone tumours, the classical lesions for such studies being epithelial tumours, soft tissue tumours, and tumours of the nervous system. With these lesions, diagnostic information is sometimes provided by the behaviour of the tumour cells in culture, this supplementing the conventional information obtained by histological examination.

Until recently, tumour transplantation has most often been made into the same species of animal—frequently the same strain—from which the tumour was obtained. It has become apparent, however, that some tumours will grow in foreign species, either in sites where they are protected from the usual immunological consequences of heterografts, or in animals where immunological reactions have been inhibited by such procedures as x-irradiation or cortisone treatment. Much work on the heterografting of animal tumours has been carried out by Greene (1941) and Greene and Murphy (1945), while more recently Toolan (1951, 1954) has been able to maintain and grow human tumours in small laboratory animals for long periods of time. A variety of tumours, including soft tissue sarcomas and epidermoid carcinomas, have been studied, while more recently a bone tumour (a chondrosarcoma of the maxilla) has been successfully grown in this way (Toolan, 1957). The tumours studied have retained their original morphology, and they are being widely used for drug screening and other biological investigations. This technique clearly deserves to be applied to a variety of bone tumours, in order to study such matters as their inherent tissue differentiation and their reactions to chemical and other therapeutic agents.

A limited amount of information is available on the transplantation of bone tumours in pure strain mice. Cloudman (1937) described the transplantation of a bone tumour which occurred in the tail of a C_{57} mouse and which was carried for 9 generations. The tumour was described as an osteogenic sarcoma, and some of the transplants showed newly-formed bone, particularly in the early generations. Barrett and his colleagues (1944) described the transplantation of an osteogenic

sarcoma occurring in a C_3H mouse, which was carried for 8 generations Transplants grew in 95 per cent of C_3H mice for the first 5 generations, and afterwards consistently in 100 per cent of animals. A slight increase in growth rate was observed during the first 5 generations, and after that a more rapid increase occurred. The primary tumour showed a good deal of bone formation, which was also seen in the first 5 generations of transplants and in pulmonary metastases in the animals carrying them. The later generations, however, failed to produce bone or osteoid tissue, and consisted of highly cellular undifferentiated spindle-celled tissue: alkaline phosphatase, which could be demonstrated in the earlier generations, disappeared This change in the properties of transplanted or cultured tumours, with the loss of the more specialized functions of the tumour cells, has been reported with many different types of tumour. Sometimes it represents a change in the inherent properties of the tumour cells themselves: on other occasions a change in the environment will show that the tumour still retains the capacity for its original behaviour. To determine the part played by the environment in the loss of bone formation in transplanted bone tumours, Hilberg (1956) studied the behaviour of a transplantable osteogenic sarcoma from a C_3H mouse which had been carried for 20 generations of subcutaneous transplants, and which had shown increasing anaplasia and ultimately total loss of bone formation. When transplants were made to the renal capsule, all of the 13 tumours developing in this situation (from 30 injected animals) showed some bone formation, while similar transplants of a fibrosarcoma were quite devoid of bone

Some transplantable tumours, which do not themselves form bone, have the ability to induce the stromal host tissues to undergo bony or cartilaginous metaplasia This appears to be the case with a carcinoma of the oviduct in a fowl, which Foulds (1937) transplanted for 12 generations, and in some transplantable liver tumours studied by Paget, Walpole and Ashton (1958) Comparison can be made with the metaplastic ossification which occurs when urinary tract epithelium is transplanted to the rectus sheath in the dog (Huggins, 1931), with the "induction" of bone and cartilage produced by certain devitalized tissues when placed under the renal capsule or subcutaneously in the ear in rabbits (Bridges and Pritchard, 1958), and—less closely—with the stimulation of stromal osteoblasts that occurs in the skeletal metastases of certain epithelial tumours, particularly those of breast and prostate.

HISTOGENESIS

In the section dealing with the classification of human bone tumours (p 159), it was emphasized that as far as the majority of these were concerned all that was known of their histogenesis was that they took origin from skeletal connective tissue With bone tumours there is little opportunity to examine the earliest lesions, or to observe their exact site of origin or the histological appearance of any abnormal tissue which may have preceded them. Such an attempt would be a meaningless exercise if a tumour had taken origin as the result of a single mutation in a previously normal cell, as there would then be no indication of any abnormal precursor. If, however, tumour formation was preceded by progressive changes involving a wider field of tissue, the examination of early tumours might well

show them to be surrounded by the changed tissue from which they had taken origin. With many tissues—particularly skin, liver, alimentary mucosa and breast—there is ample evidence that this is the case. Sometimes the precancerous changes involve the whole tissue, as with the regenerating and hyperplastic cirrhotic changes which are quite often the precursors of carcinomatous change in the liver, or they may be restricted to a particular area of tissue such as an ulcerated patch of gastric mucosa or a circumscribed area of radiation damage in the skin.

Despite the difficulty of examining the earliest lesions, it would appear unlikely that human bone tumours are commonly preceded by changes of this sort Most tumours appear to take origin in areas of bone which are histologically and radiologically normal, while there are very few non-neoplastic conditions of bone which can be shown to predispose to tumour formation. The condition of multiple hereditary exostoses has already been cited as one such condition: another is fibrous dysplasia, in which a few cases of malignant tumour—usually fibrosarcoma—have been described (Coley and Stewart, 1945; Hall, Bersack and Vitolo, 1955; Jaffe, 1946, Platt, 1947) A more important association is that with Paget's disease, and the figures already cited (p. 165) indicate that this condition is an important precursor of malignant bone tumours in old people. The great majority of bone tumours, however, develop in the absence of any demonstrable antecedent pathology, and apart from the entities already mentioned the various types of reactive or hyperplastic conditions of the skeleton—such as fracture repair, hyperparathyroidism, rickets and osteomalacia, various types of osteosclerosis, osteogenesis imperfecta and many other developmental anomalies—do not lead to the development of tumours Some malignant cartilaginous tumours appear to evolve through the increasing rate of growth of previously benign chondromas, but this is a different matter.

If, by the way, we are to regard bone tumours—or some bone tumours—as the culmination of a series of somatic mutations, it is perhaps possible that the two precancerous conditions with which we are concerned—fibrous dysplasia and Paget's disease—may prove to be abnormalities of this same character. As their nature is completely obscure, any starting point—even a speculative one—is welcome

In Paget's disease, which we must regard in its entirety as a precancerous condition, there have been occasional reports (von Albertini, 1928; Perlmann, 1934; Parenti and Ludeke, 1936) of the presence of focal areas of pleomorphic spindle-celled tissue, not apparently themselves sarcomatous, but constituting a morphological link between the abnormal Paget's bone and the frank tumours—actually multiple—which were present in the cases concerned These lesions are as near as we can get, in human pathology, to the immediate precursors of frank sarcomas: they would appear to be worth detailed study whenever they are available.

In the experimental field, however, particularly with the bone tumours produced by the administration of bone-seeking isotopes, there are a number of references to presarcomatous lesions. In commenting on tumours in rats receiving small doses of plutonium, Lisco (1956) noted that osteosarcomas sometimes arose from circumscribed areas of fibrosis occurring in the neighbourhood of damaged bone.

Owen, Sissons and Vaughan (1957), studying bone changes produced by ^{90}Sr in rabbits, noted the presence of occasional small foci of pleomorphic spindle-celled tissue which they regarded either as presarcomatous or as very early tumours. Similar tissue changes have been observed by Litvinov (1957), working with ^{90}Sr in rats, and by Kuzma and Zander (1957b) with mice and rats receiving ^{45}Ca, ^{89}Sr or ^{90}Sr, these authors also regarding them as part of the process ultimately leading to the formation of malignant tumours. Further experience of one of the present authors with these focal proliferative lesions, which are sometimes osteoblastic, and which sometimes consist merely of pleomorphic spindle-celled tissue (Owen, Sissons and Vaughan, 1959), confirms their histological similarity to more established tumours, and strongly suggests that they represent a stage in the development of the latter. It is suggested that a study of the dose-dependence of these proliferative lesions might help to define their relationship to established tumours, as might studies of tumour formation in other species and with other bone-seeking isotopes It is perhaps of interest that somewhat similar histological appearances have been encountered in the bones of rabbits developing tumours as a result of the administration of beryllium compounds (Barnes, Denz and Sissons, 1950), the tumours apparently arising in areas of medullary fibrosis.

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ABSTRACTS RELATING TO ORTHOPAEDIC SURGERY

A SURVEY OF THE BIOLOGICAL PROPERTIES OF TUMOURS OF BONE

Tumours of bones and joints

A systematic account of bone tumours, mainly from the point of view of the histopatho-

radiological findings, followed by a detailed account of gross and microscopic pathology and a discussion of differential diagnosis. The overall emphasis is on diagnosis, but for each type of tumour there is a brief section on treatment. The book describes in detail the various entities, such as osteoid osteoma, benign chondroblastoma and chondromyxoid *fibroma, the recognition of which we owe to Jaffe and his colleagues at the Hospital for*

primary bone tumours Lesions of the jaw bones and bone tumours occurring as a result

recur locally if not completely removed

lesions, particularly synovial sarcoma a

Malignant tumours of bone and cartilage

Sissons *(1958)* gives a brief account of the pathology of the main types of malignant tumours of skeletal connective tissue—

giant-cell tumour. Parosteal osteosarc

group because of its better prognosis

irradiation damage to bone are discu

Primary bone-forming tumours

Relationship to skeletal growth

Price (1958), using information from the *British Bone Tumour Register*, the British Empire Cancer Campaign (1949), Stocks and Barrington (1925), Meyerding (1927) and Geschickter and Copeland (1949), studied primary bone-forming tumours and

...a. The multiple ...at its document- ...be synonymous ...arising in bone: ...chondrosarcoma

was included in the study as being a variant of osteogenic sarcoma in which most of the

tumour tissue is neoplastic cartilage. Such tumours often form bone, sometimes extensively. Analysing the figures from various sources it was found that both solitary osteo-

th sexes tumours appear to
upper arm than in those of
growth is thought to be the
cause of each type of tumour. Price considers that the greater growth of the male, and the differences in skeletal development in the two sexes, offer a simple and reasonably consistent explanation of the peculiarities of distribution and incidence of the two types of lesion, and make it possible to discern the interplay of the three factors of age, sex and site of origin of the tumours.

Chondromyxoid fibroma of bone

IWATA and COLEY (1958) review the 30 cases of chondromyxoid fibroma of bone described in the literature, and report 6 further cases from the Memorial Cancer Center, New York This rather rare tumour, originally described by Jaffe and Lichtenstein in

malignant change occurring in this type of tumour. The patient concerned was a male aged 17 years with a recurrent tumour of the fibula. Twelve months previously part of the fibula had been resected for a tumour, and a histological diagnosis of chondromyxoid fibroma made on the resected specimen. Further local resections showed the histological appearance of low-grade chondrosarcoma, and the leg was ultimately amputated The patient was well 20 months later (The histological structure of this tumour is, unfortunately, not illustrated.)

Malignant angioblastoma of bone

CHANGUS, SPEEI
angioblastoma of
adamantinoma of

a specimen containing endothelial angioblasts, but mesenchymal angioblasts prominent. About 7 years later additional sections of the original tumour sho typical features of a malignant angioblastoma. When the leg was amputated the scopic pattern of the tumour was chiefly that of a mesenchymal angioblastom alkaline-phosphatase histochemical reaction was found to be positive in those angi which were differentiating into tumour endothelial cells. In 2 of 4 cases well-differen endothelial angioblasts gave a strong alkaline-phosphatase reaction, whereas the epit cells of 2 adamantinomas of the jaw yielded negative reactions. The authors consi to be unfortunate that the tibial tumour examined by Fischer in 1913 was regarde identical with adamantinoma of the jaw, so far as its microscopical appearances w concerned Examination of the literature showed that 25 of 27 "adamantinomas" of long bones could be reclassified as malignant angioblastomas.

Chordoma

Staining reactions

CRAWFORD (1958) gives an account of the staining reactions of material obtained from 6 cases of chordoma, with special reference to differential diagnosis. In 1 case the chance occurrence of pulmonary metastases facilitated direct comparison between the reactions of chordomatous metastases and the reactions of normal bronchial cartilage In another case the presence of pulmonary metastases from a chondrosarcoma allowed a similar comparison to be made with neoplastic cartilage. Mucin stains gave positive acid-mucopolysaccharide reactions with both chordomatous and cartilaginous ground substance, and it was not possible to distinguish the two types of tumour using such staining procedures. A sharp distinction was obtained, however, with the reticulin and the phosphotungstic-acid-haematoxylin stains, which produced strong impregnation of the cartilaginous ground substance but failed to stain the chordomatous matrix. The reticulin stain produced a heavy deposit in normal and neoplastic cartilage. Cells were outlined sharply, but precipitation in the intervening ground substance was more diffuse. Crawford concludes that the reacting substances in cartilaginous and chordomatous tissue belong to the category of acid-mucopolysaccharide. When the presence of chordoma is suspected and physaliphorous cells cannot be found in the section, the absence of staining of the ground substance with the reticulin and phosphotungstic-acid-haematoxylin techniques may be of diagnostic value. The physaliphorous cells of chordoma contain numerous clear vacuoles of varying size. The matrix presents a similar vacuolated appearance. If the cells collapse, biopsy may lead to the erroneous diagnosis of chondrosarcoma, especially when the tumour occurs at an unusual site such as a spinal vertebral body.

Radioactivity and the human skeleton

An interesting attempt to evaluate the danger of exposure of the skeleton to radioactive materials by means of a consideration of the incidence of bone tumours in populations known to have a relatively high "normal" skeletal content of radium, is presented by MARINELLI (1958) The "normal" radium of bone is ingested with food and water: in the U.S.A. the contribution of food is small, and the skeletal "burden" of radium depends largely on the concentration of naturally occurring radium in the water supply. The radium content of the water supply of the city of Chicago is low, and the estimated skeletal burden is 0.4×10^{-4} microcuries: in some nearby communities the values are much greater, the estimated skeletal burden being about 7.0×10^{-4} microcuries In the Chicago (low radium) area the annual mortality from "bone cancer" is 1·78 per 10^5 population, while in the other (high radium) areas the figure is 2·17 per 10^5. The difference is hardly to be regarded as statistically significant, but it is suggested that further studies of radium body burden and bone tumour incidence in other relevant populations should be carried out. Other groups are also considered, where far greater body burdens have resulted either from industrial exposure in the course of painting luminous dials, or from the administration of radium for supposedly therapeutic purposes. About 190 such cases

are described in the literature. In a Boston group, consisting of 30 patients and dial-painters, the body burden of radium averaged 5·4 microcuries and the bone tumour incidence was roughly 1,200 times the normal. In similar groups from Chicago and Elgin, the average body burdens were 2·6 microcuries and 1·5 microcuries, and the incidence of bone tumours was respectively 840 and 310 times the normal. Interest is also expressed in the bone tumour incidence in certain groups of people exposed to abnormally high amounts of other radioactive materials or ionizing radiations. The first of these consists of patients who in past years have been injected with thorotrast for diagnostic purposes. The second consists of fairly large populations in India and Brazil living over thorium-containing sands and thus receiving a high "background" radiation. The third consists of populations living at high altitudes and thus receiving relatively high doses of cosmic radiation than other populations. It is suggested that information on the bone tumour incidence in these groups of people, as well as in groups with differing natural radium intakes, may be of great importance in assessing the danger of exposure to small amounts of other radioactive materials—particularly the ^{90}Sr now present in the environment as a result of the testing of atomic weapons

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PROGRESS IN AMPUTATIONS

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SITES OF ELECTION

Substantially, the sites of election for upper and lower extremity amputati adults remain as indicated by Perkins (1947) and where bone section is necessi there has been no reason for their amendment.

Lower extremity

Since the end of World War II, experience has emphasized the value of operations in the lower extremity which can now be regarded as additions t number of "ideal" sites when conditions permit their being performed. The the disarticulation at the knee and the true Syme amputation.

In the upper extremity disarticulation is usually a method of second choice is considered a bad one at that, but in the lower extremity, disarticulation a hip, knee or ankle may often be an alternative of equal value to amput through femur or tibia.

In the past 12 years or so there has been a noticeable increase in the numb amputations of the lower extremity amongst elderly people with vascular di and diabetes mellitus. In many of these a below-knee amputation is often formed in the first instance. In such cases the level of bone section of the tibi matter of considerable importance if the amputation be a definitive one longevity of the stump is considered A number of tibial stumps in exce 5½ inches have failed. Whilst, as was stated by Perkins (1947), "the stump shoul long enough to give adequate function and short enough to provide good cir tion" the compromise between these two in the cases now under consider should, it is felt, be found at a length shorter than usually adopted and sh not exceed 4 inches. Little, if any, function is lost thereby owing to the impr

methods of fitting very short tibial stumps and the risk of having to re-amputate above the knee at a later date is lessened.

Upper extremity

With regard to amputations of the upper extremity, the sites hitherto regarded as ideal so remain.

There have, however, been a number of cases in which amputation through the humerus has had to be performed for brachial plexus injuries In such cases it has been found that the best function results from a bone section of the humerus giving a 7-inch stump from the tip of the acromion process and with the shoulder joint arthrodesed in slight flexion and abduction

Guillotine amputations

Guillotine amputations have been rendered unnecessary since the advent of antibiotics. Flaps should always be cut, as in a definitive amputation, and lightly sutured with a few skin sutures, or they can be left fully open—to be closed by delayed primary suture in 4–5 days. Excellent drainage can be obtained in these circumstances. This does not leave a huge raw surface and secondary suture becomes unnecessary. Skin traction after guillotine amputations as a rule proves unsatisfactory, and when an unhealed area is subsequently grafted the stump does not prove durable.

DISARTICULATION AT THE KNEE

When femoral bone section is not essential and when there is sufficient viable skin to provide adequate flaps, a disarticulation at the knee should be preferred to the so-called ideal 10–11-inch stump.

Advantages

The advantages are speed of operation, no interference with the crucial anastomosis, no section through muscle sheaths, and the provision of a natural end-bearing surface gives a proprioceptive sense of balance and position

It is found that patients fitted with an artificial limb after a knee disarticulation more rapidly acquire balance and their period of training is less than it is with those who have undergone amputation through the femur

The retention of the epiphysis at the lower end of the femur in children is obviously a great advantage.

Indications

This operation may be rapidly performed with minimal blood loss It is, therefore, indicated in desperately ill patients, particularly those with multiple injuries including crushing of the legs and feet

The operation is also indicated in those amputation cases where it is impossible to do an adequate below-knee amputation and yet there is sufficient skin available to perform a disarticulation of the knee and cover the condyles with healthy skin The operation sometimes proves useful in elderly patients

Surgical procedure

Full details of surgical procedure have been given by Gillis (1958a)

DISARTICULATION OF THE ANKLE
(SYME'S AMPUTATION)

Indications

The Syme operation performed under perfect conditions provides a stump which is known to survive with end-bearing for over 40 years. It is indicated in injuries of the forefoot which leave the heel-flap skin intact. It may also be used for chronic disease of the foot and toes. The operation became unpopular in England after World War I when many Syme's amputation stumps broke down. In Scotland and in Canada, however, it never fell into disrepute. There is some evidence that the poor results in World War I were owing to the use of this operation in patients with trench foot when the heel flap was involved by the vascular abnormality.

Contra-indications

This operation should not be used in patients with peripheral vascular disease. When the ankle pulses are present a transmetatarsal amputation is preferable and when they are absent a Syme's amputation seldom if ever heals satisfactorily.

Surgical procedure

Full details of surgical procedure have been given by Gillis (1958b).

AMPUTATIONS FOR REMOVAL OF CONGENITALLY MALFORMED EXTREMITIES

In dealing with young persons the principle of conservatism should apply and amputation be withheld, always provided that, in lower extremity cases, the child can be rendered ambulant by some form of extension prosthesis.

If the latter proviso holds good then it is better to defer amputation until such time as the child attains the age at which he can decide for himself. In a number of instances, particularly girls, amputation has been asked for during adolescence when they can appreciate the implications.

Conservative procedures, such as excision of abnormal and deformed joints, osteotomies and division of contractures, often result in a useful and serviceable, albeit short, limb which can be fitted with an extension prosthesis until such time as a definitive amputation may become necessary.

AMPUTATIONS FOR TRAUMA OR DISEASE IN CHILDREN

Unlike the policy adopted towards adults, it cannot be said that there are any ideal sites or stump lengths where bone section is necessary.

Lower extremity

When circumstances permit, in children it is especially useful to perform a disarticulation at the knee, thus conserving the lower femoral epiphysis, or a Syme's amputation, thereby conserving the lower tibial and fibular epiphyses. When adolescence is reached, the Syme's amputation enables the patient to be fitted with a standard below-knee prosthesis, if the limb has not developed *pari passu* with the sound leg, without the necessity of further surgery

Whenever bone section is contemplated the guiding principle should be to amputate at the lowest possible level. When the amputation is below the knee it is advisable to cut the fibula slightly shorter than in adults, owing to the more rapid growth of this bone.

Upper extremity

For amputations of the upper extremity, while the same general principles already given for adults apply, the lowest possible bone section should be aimed at For amputations above the elbow, more generous flaps are advisable because of the rapid growth of the humerus which in due course tends to pierce the skin, producing the so-called conical stump of children, and necessitates re-amputation.

PREPARATION FOR ARTIFICIAL LOWER LIMB

After the amputation, the team, consisting of nurse, physiotherapist and surgeon, continue their task of preparing the stump for fitting with an artificial limb, and so treating the patient mentally and physically that he can use the amputation stump and artificial limb to the utmost value.

Preparation of the stump

Besides re-education and development of stump muscles to the maximum possible extent by exercises and pylon wearing, post-operative treatment is concerned with dispersal of terminal oedema

Modelling stumps by elastic stump socks

A well-healed and durable stump can quickly be produced by this method, which is now superseding stump bandaging

Elastic stump socks are made from two-way stretch material, woven to give maximum pressure at the distal end of the stump The advantages of elastic socks are as follow (1) they exert an even pressure (reducing the oedema), (2) they do not produce folds or invagination of the skin, and thus do not leave furrows; (3) they shape the stump in a conical manner and produce an even contour leaving a linear scar, (4) the employment of these socks prevents any injury to the stump which may occur as a result of inexpert bandaging, (5) the patient can apply and adjust the socks himself; (6) the socks are not cumbersome, require no bandaging and save the time of the physiotherapist

Stump socks are made in two types, one set for above-knee amputations and another for below-knee amputations; each set is produced in three graded sizes—small, medium and large. The small below-knee socks are also suitable for arms.

They are easily washable, are economical and can be used by the patient at night as well as by day.

PROSTHESES

Temporary prostheses

Lower extremity amputees

The purpose of a temporary prosthesis or pylon is twofold. First, to render the patient ambulant as soon as possible and, secondly, in certain cases to test his reaction to limb wearing or experiment with fittings. Pylons are all the more necessary in these days owing to the long time taken to manufacture a permanent limb, a pylon being made in little more than two weeks.

In earlier days the term pylon meant a plaster of Paris socket and in those areas where there are no nearby limb fitting facilities such sockets are still made, but ideally the sockets are made by a limb maker of either Durestos or duralumin, the latter being the better

The shape of pylon sockets, which should be the same as for the permanent limb later to be supplied, is, for all suitable cases, the anatomical shape as opposed to the older conical shape The side struts of the pylon are either of ash or of duralumin and the peg base, instead of being circular with a Phillips' rubber screwed on, is now of the rocker type which has proved most beneficial.

One objection to the pylon in the past has been the fact that there is no knee joint and patients cannot travel in public transport or sit in confined places in comfort. Field trials are now taking place with articulated pylons to overcome this objection.

Patients with below-knee amputations whose stumps are for various reasons not quite ready for a below-knee limb but who should be rendered ambulant as soon as possible are now being fitted with pylons as for above-knee amputations with the below-knee stump held in a webbing sling.

Forearm amputees

It is important that the arm amputee should begin to make use of the stump as soon as possible after amputation, otherwise there is a tendency to become one-arm minded. Plaster socketed forearms are now made into which appliances can be fitted and some arm training be given whilst waiting for the permanent arm to be made

Articulated permanent prostheses

During the last 12 years development has taken place in the fitting and design of artificial legs.

The fitting of sockets

Above-knee limbs.—For years, sockets for above-knee stumps have been of the conical shape with a gluteal shelf which slopes forwards and inwards. With these there was a tendency for the ischial tuberosity to slide within the lumen of the

socket resulting in a "plug fit" with in some cases the production of a roll of tissue and all that results therefrom—for example, epidermoid cysts and "choked" stump The anatomical socket which is now a standard issue for suitable cases has a low back with a flat ischial seat and with adequate channelling for the adductor longus tendon and muscle, whilst the metal below the brim posteriorly is belled out to accommodate the extensors. Great improvement has resulted from their use as they maintain a healthy stump, and there is absence of rolls of flesh, epidermoid cysts and similar complications.

Below-knee limbs.—For those patients whose stumps demand full ischial bearing, the older type of ischial bearing corset did not prove to be sufficiently positive in some cases, and the tuberosity would slip down within the corset, allowing too much pressure upon the stump For these patients, corsets are now made of heavily blocked leather, sometimes reinforced, of the same shape as described above for above-knee stumps.

Hip disarticulation —A new shape of socket based upon an idea introduced and used by the Canadian Limb Service has been used for a number of cases now undergoing field trials The position of the artificial hip joint is placed more anteriorly, giving an improved sitting position; the socket shape embraces the whole pelvis and provides excellent control of the limb and avoids the need for any shoulder suspension. Experiments are being carried out using a moveable hip joint.

Hindquarter amputations.—A number of patients having suffered this severe operation have been successfully fitted with limbs of the usual tilting table type but with the base of the socket carried medially to enable a bearing to be taken upon the contralateral ischial tuberosity. In a number of instances these patients are leading active lives.

The design of above-knee limbs

Criticisms have been made from time to time regarding the lack of stability of patients, particularly the elderly, wearing above-knee limbs. Two methods are now available to overcome this

The forward set thigh.—Normally for all above-knee limbs the position of the transverse knee bolt is set ¾ inch posterior to dead centre of the knee piece; this provides stability for the active younger person who is trained in the use of his hip extensor muscles. For many, however, this is insufficient and for them the socket and thigh of the limb are set ¾ inch forward of dead centre giving the additional stability

The semi-automatic knee lock.—There are many elderly above-knee amputees who will never acquire sufficient strength or confidence to walk on the limb with a free swinging knee and will always walk with the knee locked. For these the semi-automatic knee lock has been designed and is routinely used. To sit down the patient presses a knob on the thigh piece which enables the knee to flex for sitting down but on standing erect the knee automatically locks in extension.

Suction sockets

The fitting of suction sockets became dormant in Great Britain in 1928 but was revived in 1946. Though some hundreds of patients have been supplied successfully and those so supplied will never return to a standard type of limb, the general interest has been of very slow growth.

Sockets are now made in either willow wood or Alclad (aluminium-covered duralumin) and the fitting is strictly anatomical. A two-way valve is used which ensures that, when properly adjusted, the negative pressure at the stump extremity never exceeds 1½ pounds per square inch. Whilst any femoral stump long enough to control a standard above-knee limb can be considered for suction provided there is no bad scarring or adhesion to deep tissues, no anaesthesia or liability to skin eruptions, success depends very largely, if not entirely, upon the most careful selection and briefing of the patient.

The patient must evince a real desire to avoid pelvic or shoulder suspension and be of the personality to persevere against initial set-backs, and appreciate the need for extra fittings and more frequent adjustments for the first year or so. He must also, if employed, be able to attend the limb centre when required without risk of loss of employment. Some have had to give up the suction limb for the latter reason, others through lack of patience or determination. The suction principle is particularly applicable to women, amongst whom there have been few, if any, failures. At present suction is used only for above-knee amputees.

Artificial legs for children

Amputation cases.—Artificial legs are supplied to children from the age at which they show signs of trying to stand and walk. For infants and very young children up to the age of about 8 years, wooden limbs are normally supplied, being quicker to adjust and lengthen as needed. The legs are miniature replicas of the adult limb except that there is no mechanical ankle joint, which saves weight, and the foot and ankle are in one piece and rigid with the forepart of the foot made of compressed felt. After the age of 8 years, consideration is given to the incorporation of more mechanical features such as proper ankle joints, adjustable knees and so forth, and the wood limbs may be replaced by metal.

The follow-up of children is most important and they should be seen every 3 months at least to check growth and stump change.

A child who in infancy has undergone a Syme operation can in due course be fitted with the standard limb for below-knee amputation with end-bearing.

Non-amputation cases.—Very many children suffering from congenital malformations, single and bilateral, and those suffering from the effects of poliomyelitis with shortening and varying degrees of equinus are now being fitted with extension prostheses; the deformed or useless foot is enclosed within a soft leather bootee below which is fitted an artificial foot with or without an ankle joint.

Many other activities concerning the development and improvement of prostheses are being engaged in by the Research Department, Queen Mary's (Roehampton) Hospital, and amongst them are included the following which are undergoing field trials.

A stabilized artificial knee joint for above-knee limb wearers has been undergoing field trial for some time. This enables a patient to bear his whole weight on the artificial knee when it is flexed to 30° and thus it prevents falls when he stumbles. A polycentric knee joint for below-knee amputees has been in use with great surgical benefit for many years: it most nearly represents the movement of the natural knee. Mechanically, however, it does not always prove satisfactory. A new design is now being tested. An artificial ankle joint which permits of flexion and extension, lateral movement and a torsional movement is being tried out by a number of patients. Work has also started on the production of plastics for artificial limbs.

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ABSTRACTS RELATING TO AMPUTATIONS

Upper-extremity prostheses

Age of fitting in children

McDONNELL (1958) reports on the fitting of [illegible]

a standard forearm piece and a [illegible]

readily learned how to operate the terminal device Prosthetic tolerance was obtained even in the youngest child, and functional patterns were facilitated for movements requiring the use of both hands During the course of the investigation it was not possible to evaluate either the psychical reaction to early prosthetic fitting or the masking of the sensory function of the deformed extremity.

Reconstruction of amputated thumb

MIKHAIL (1958) describes the reconstruction of the amputated thumb by means of tubular skin and bone grafts. Under
size and including the fatty layer of
abdomen and then sutured back. Af
is tubed with the patient under gener
rupted at one end and transferred to the prepared recipient site. Elastoplast and padding are used for fixing the extremity and the sutures are removed on the tenth day. The tube is detached from the abdomen 4 weeks later. The edges of the tube are excised and flaps are made so as to give the appearance of a thumb. A splint is applied to prevent kinking and 2 weeks later the tube is supported by a bone graft derived from the seventh rib. Care is taken to include the outer periosteum in the rib segment, but the borders of the segment are excised in order to encourage revascularization. A tunnel is made in the receiving bone, the rib segment is inserted and the tubular graft is sutured into position. External splinting is required for 2–4 months. The author reports on 3 cases in which the reconstruction operation was employed. One of the patients, a carpenter aged 29 years, was able to resume his work after a period of 4 months, when movements of the reconstructed thumb were found to be excellent. The bone had united well and full sensation had been acquired.

Double above-knee amputation

Rehabilitation of the elderly patient

LOWENTHAL, POSNIAK and TOBIS (1958) state that during a period of 5 years, 49 elderly patients with bilateral
diseases
arterioscler
for the peri
when pylon
importance
the physiol
impaired function of th
proved to be a major ca
despite the fact that the device offers the advantage of lowering the centre of gravity,

a trend towards reduction in insulin intake It appeared that positioning was only one of

relatively favourable status may achieve much less than a patient who is severely handicapped by senility and disease.

Syme amputation

Evaluation

A Syme amputation was performed 1 year later and subsequently the boy successfully wore a weight-bearing prosthesis. A good functional result was obtained in a girl aged 4 years whose right lower extremity was 3 inches shorter than the left at the time of the

amputation. She was able to wear an end-bearing prosthesis with a knee-strap. End-bearing prostheses also proved to be adequate after the amputation had been performed

ensure the greatest possible area for support of the heel flap the tibia should be cut through its largest cross-section In the case of women, however, the bulbous appearance of the ankle can be avoided by adopting Elmslie's modified technique in which the tibia is divided ¾ inch above the articular surface. The amputation is indicated in destructive lesions of the foot (provided that an inch of the heel has sensation and blood supply), in deformities causing shortening of the lower extremity and in selected cases of obliterative vascular disease. As compared with the below-knee amputation the Syme amputation permits full weight bearing at the end of the stump and allows a gait pattern which is almost normal.

Lower extremity amputations for arteriosclerosis

CLAUGUS and his colleagues (1958) review a series of 89 cases of senile and diabetic arteriosclerosis in which amputations were performed on the lower extremity. The patients were males belonging in most instances to the age-group of 50–70 years. The age-incidence of patients with diabetes mellitus showed no significant variation from the age-incidence of non-diabetic patients Many patients had suffered from cardiac disease and were in a poor state of nutrition With regard to the site of amputation, the operation was performed above the knee in 71 cases and below the knee in 47 cases Successful results were obtained in 70 and 41 cases, respectively. For the major amputations there was a patient mortality of 6 1 per cent. The operation mortality was 4 2 per cent The post-operative deaths were 5 in number and occurred among the series of patients with amputations above the knee. Nearly one-quarter of the number of patients died within the first two post-operative years Indications for amputation included gangrene, uncontrolled pain at rest and uncontrolled infection Sympathectomy was often performed prior to amputation For the latter operation spinal anaesthesia was administered in the majority of cases No tourniquets were needed A fish-mouth type of incision was adopted for toe amputations and the McKittrick technique, with a long plantar flap, was used for trans-metatarsal amputations Below-knee operations were performed with the patient in the prone position As for operations above the knee, equal short anterior and posterior flaps were constructed in order to conserve the maximal blood supply The muscle flap was ⅛-¼ inch shorter than the skin flap and the bone was sawn at the level of the apex between the skin flaps. The wound was closed without drainage

Tumours of the bony pelvis

Resection and radical amputation

MONRO (1958) believes that resection of a segment of the pelvic girdle may be the

investment of normal tissue is no longer intact The case is recorded of a man, aged 21 years, with an exostosis arising from the posterior surface of the body of the pubis

resected with the tumour. The gap in the medial part of the wound was closed temporarily with a double-layered sheet of tantalum gauze. Full movement at the hip was noted 10 days after the operation. The wound healed soundly and never caused any disability. Eventually the patient was able to balance on the right leg and to carry out tasks requiring a high degree of strength and agility.

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ENDOCRINE ASPECTS OF GYNAECOLOGY

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NORMAL FLUCTUATIONS IN SEX HORMONE SECRETION

The development of more accurate methods of urinary oestrogen estimation by Brown (1955) and of pregnanediol excretion by Klopper (1957) has led to a revision of some of the concepts of the endocrine changes during the normal menstrual cycle.

Oestrogen in the form of oestradiol-17β and oestrone is secreted throughout the entire menstrual cycle. The maximum endogenous production occurs at the time of ovulation (the "ovulatory peak") when on the average 57 micrograms of total oestrogen are excreted per 24 hours. A second ("luteal") peak averaging 33 micrograms per 24 hours extends over the eighteenth to twenty-fifth days During the immediate premenstrual period the oestrogen levels fall rapidly and by the first day of menstruation the average daily excretion is 12 micrograms (*see* Fig 43) (Brown, Kellar and Matthew, 1959)

Progesterone is also produced throughout the menstrual cycle The adrenal cortex is the source of the basal secretion and, following the development of the corpus luteum, an additional quantity is produced by this structure, with a peak output about a week following ovulation. The concentration of progesterone, as determined by estimating urinary pregnanediol, then falls off to reach the basal level by the time of menstruation (Fig 44)

In the human being it has not been possible to separate follicle stimulating hormone secretion from luteinizing hormone activity. These are probably two manifestations of the one pituitary gonadotrophin There is a steady production of pituitary gonadotrophin throughout the menstrual cycle with, in some cases, a mid-cycle peak. The gonadotrophin peak occurs just after ovulation and the first oestrogen peak, but before the rise both in urinary pregnanediol and in basal body temperature (*see* Fig. 45) (Brown, Klopper and Loraine, 1958).

OESTROGEN PREPARATIONS

Oral administration

Oestrogens are most conveniently administered by mouth. Stilboestrol is still the oral oestrogen of choice. Ethinyl oestradiol weight for weight is twenty times more

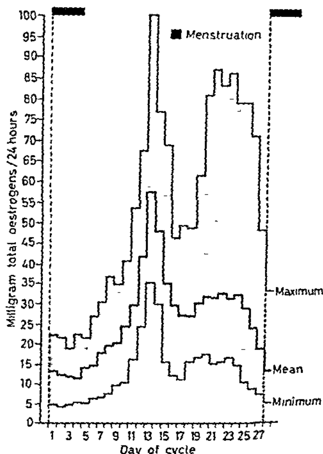


FIG. 43.—Mean maximum and minimum levels of total urinary oestrogens from 16 women, aged 18–41 years, with normal menstrual cycles. Time between onset of bleeding (day 1) and ovulatory peak of oestrone/oestradiol varied from 10 to 18 days (mean 13 days) and between oestrone/oestradiol ovulatory peak and first day of next

active than stilboestrol but is more expensive and possesses no significant advantage over stilboestrol. Dienoestrol is one-fifth and hexoestrol one-twentieth as active as stilboestrol.

In menstruating women equipotent doses of all these oral oestrogens produce nausea if given in amounts in excess of the equivalent of 3 milligrams a day of stilboestrol However, the tolerance to oestrogens is proportional to the endogenous oestrogen production Pregnant and recently delivered patients are rarely upset by oestrogens, while postmenopausal women may experience nausea with 1 milligram stilboestrol daily If a patient persists in taking large doses of oestrogens the nausea often wears off

Parenteral administration

Oestradiol, the hormone produced by the ovary, is available as the monobenzoate (or similar ester) for injection, either in oil or as an aqueous suspension Oestradiol

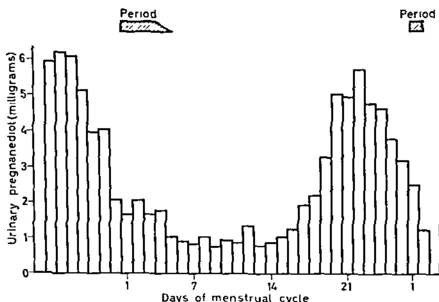


FIG. 44 —Pregnanediol excretion in the normal menstrual cycle E.M , aged 28 years, para 2+0 (By courtesy of the Editor of *The Journal of Obstetrics and Gynaecology of the British Empire.*)

benzoate, 5 milligrams, given twice weekly by injection, produces the same effect as 1–2 milligrams of stilboestrol given daily by mouth The following oestrogens are available for parenteral use·

Intramuscular injection of oestradiol monobenzoate is effective for 3 days
Intramuscular injection of oestradiol dipropionate is effective for 3+ days.
Intramuscular injection of oestradiol valerate is effective for 20 days
Intramuscular injection of oestradiol cyclopentyl propionate is effective for 20 days
Intramuscular injection of oestradiol microcrystals in aqueous suspension is effective for 14–21 days
Stilboestrol implant of 50–100 milligrams is effective for 3–5 months
Oestradiol pellet 50–100 milligrams is effective for 9–12 months.

PROGESTATIONAL STEROIDS

Classification

Progestins fall into two groups: those used parenterally and those usually given by mouth.

Pare.

Oral compounds showing progestational activity

17 α-ethinyl-testosterone (anhydro-hydroxy-progesterone) (ethisterone)
17 α-hydroxy-progesterone-17-acetate
9 α-bromo-11-keto-progesterone (Braxarone)
17 α-methyl-19-nor-testosterone
17 α-ethyl-19-nor-testosterone (Nilevar)
17 α-ethinyl-17 hydroxy 5(10) estren-3-one (norethynodrel)
...adiol (Enavid)

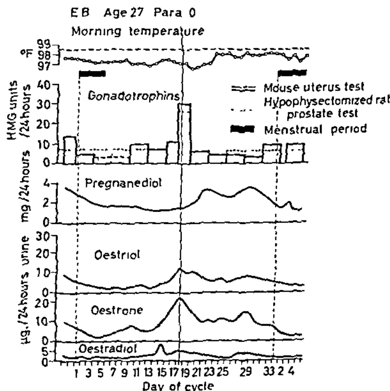


FIG ... pregnanediol, oest ... variations in bas ... onadotrophins. ... crinology.)

Chemistry

Methyltestosterone is an androgen with no progestational activity. Removal of the methyl radicle at C_{19} results in 17α-methyl-19-nor-testosterone which has

progestational activity as well as being androgenic. Addition at C_{21} of an ethyl or ethinyl radicle increases progestational and decreases androgenic activity

Progestational steroids β oriented at C_{17} and with a ketone group at C_{20} are catabolic, natriuretic and chloriuretic. Progesterone, 17α-hydroxy-progesterone, 17α-acetoxy-progesterone, and 17α-hydroxy-progesterone caproate belong to this group.

When the C_{17} side chain is in the α position, progestational compounds tend to be anabolic and salt retaining (Landau, Lugibihl and Dimick, 1958).

Ethinyl-testosterone, ethinyl-19-nor-testosterone and ethyl-19-nor-testosterone are members of this latter group

Physiological action

The progestational steroids, although producing physiological effects very similar to progesterone, do not mimic its action in all respects.

Antigonadotrophic action

Pincus, Rock and Garcia (1958) have claimed that all these steroids, in adequate doses, inhibit the secretion of gonadotrophins by the anterior pituitary, thus preventing ovulation in the female and producing azoospermia in the male. On cessation of therapy, gonadotrophin secretion for a short time may occur at a higher level than before (rebound effect), resulting in more consistent ovulation or a higher sperm count than before the start of treatment.

Oestrogenic action

Enavid is a mixture containing 1 5 per cent of an oestrogen Its oestrogenic effect by injection is similar to 10 per cent of the activity of oestrone. By mouth the oestrogenic potency is only one-third that obtained following parenteral administration.

Nor-ethisterone acetate is sometimes dispensed in 2 milligram tablets which also contain ethinyl oestradiol 0 01 milligram

Androgenic action

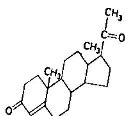
17α-ethinyl-nor-testosterone (Nor-ethisterone; Norlutin) and norethynodrel (Enavid) have an androgenic action similar in magnitude to that of 17α-ethinyl-testosterone (ethisterone) Large doses of these hormones should not be administered during the first half of pregnancy on account of the risk of producing pseudo-hermaphroditism if the foetus is female

Anabolic effect

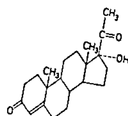
Ethinyl-nor-testosterone (Nor-ethisterone) and ethyl-nor-testosterone (Nilevar) are anabolic and produce mild sodium retention. The anabolic effect of ethyl-nor-testosterone is similar to that of testosterone propionate.

Effect on the endometrium

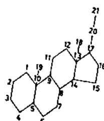
If progesterone administration is continued in adequate dosage for more than 14 days from the time of ovulation, early decidual changes occur in the endometrium Similar effects are produced when orally active progestins are administered

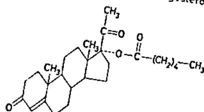


Progesterone

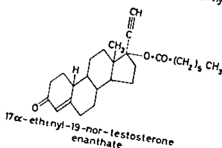


17α-hydroxy-progesterone

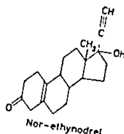




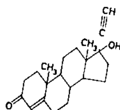
17α-hydroxy-progesterone-17-n-caproate
(Delalutin)



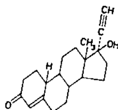
17α-ethinyl-19-nor-testosterone
enanthate



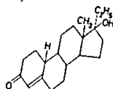
Nor-ethynodrel



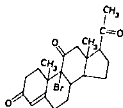
Anhydro-
17β-hydroxy-progesterone
(Ethisterone)
Ethinyl-testosterone



17α-ethinyl-
19-nor-testosterone
(nor-ethisterone)
(Norlutin)



17α-ethyl-19-nor-testosterone
(Nilevar)



9α-bromo-11-keto-progesterone

for more than 2 weeks. If, for example, Enavid is administered from the fifth day of the cycle, the endometrial glands undergo changes normally seen during the 5 days following ovulation and then gradually regress, so that after 20 days of medication, they closely resemble glands found on the fifth day of a normal cycle. Generalized oedema of the functional layer of the endometrium, typical of the week following ovulation, appears after the first few days of treatment. In the normal menstrual cycle this oedema begins to subside 7 days after ovulation, but with 19-nor-testosterone medication, the oedema persists with gradual declination to the sixteenth day of medication The predecidual cytoplasmic enlargement of the stromal cells starts on the seventh day of steroid ingestion and progresses rapidly. After 11 days of steroid administration, the stromal cells resemble those seen normally 12 days after ovulation. After 17 days of steroid ingestion, the stroma closely resembles that associated with an early pregnancy.

In the oestrogen-primed female, two intramuscular injections each of 125 milligrams of 17α-hydroxy-progesterone caproate (Delalutin) 7 days apart combined with a long-acting oestrogen will induce a well-developed secretory endometrium, indistinguishable from that of the normal post-ovulatory phase.

With the very large doses of 17α-hydroxy-progesterone-caproate, the endometrial glands show only the characteristics of the proliferative phase, some cases develop atrophic endometrium and the vaginal smear shows evidence of oestrogen deficiency.

The normal cyclic menstruating endometrium is more sensitive to progesterone and progesterone-like compounds than the endometrium found in secondary amenorrhoea.

Effect on the testis

Heller and his colleagues (1958) studied the effect of progesterone (50 milligrams daily by intramuscular injection) and ethyl-nor-testosterone (Nilevar), ethinyl-nor-testosterone (Norlutin) and ethinyl-hydroxy-oestren-3-one (Enavid) in doses of 30 milligrams a day by mouth on healthy male volunteers The Norlutin contained 0 35 per cent and Enavid 1·5 per cent of the 3 methyl ether of ethinyl oestradiol

All four compounds produced a reduction in sperm count and sperm motility. Norlutin and Enavid produced azoospermia in 7 weeks, Nilevar in 8 weeks and progesterone in 10 weeks

With both Norlutin and Enavid the biopsy specimens from the testis showed few mature forms, but with Nilevar and progesterone, the number of spermatocytes, spermatids and sperms made it difficult to reconcile the state of azoospermia with the morphological picture At the end of the treatment the testicular size was reduced in nearly every subject.

Following withdrawal of therapy, the sperm count of all groups remained depressed for about 12 weeks, when an abrupt rise occurred resulting in sperm counts higher than those obtained before the administration of the steroids.

The subjects taking the oral progestins all gained weight and experienced a subjective improvement in well being Those receiving progesterone did not gain weight and complained of increased irritability and fatigue Gynaecomastia

occurred frequently among those taking Enavid and progesterone but was only minimal in those on Nilevar and Norlutin.

After 3–4 weeks of treatment all subjects noted a complete loss of libido but this reappeared within 1–2 weeks after the withdrawal of therapy and by 6 weeks was at the pretreatment level in every case.

Urinary gonadotrophin and pregnanediol levels were unchanged, while 17-ketosteroid (probably of adrenal origin) excretion was decreased. Following withdrawal of therapy, gonadotrophin excretion in the urine showed a transitory increase

Enavid produced almost complete abolishment of the Leydig cells. This eff was not quite so marked with Norlutin, was less evident with Nilevar and lea with progesterone.

Effect on basal temperature

The action of the progestational steroids is similar to that of progesterone in producing an elevation of the basal body temperature.

Effect on pregnanediol excretion

About 10 per cent of progesterone is excreted in the urine as pregnanediol. The progestational steroids are not excreted in the urine as pregnanediol but their ability to suppress endogenous progesterone production by the ovary is shown by the reduction in pregnanediol excretion which follows their administration. A proportion of 17-hydroxy-progesterone caproate is metabolized to pregnanetriol which is excreted in the urine.

Effect on 17-ketosteroid and 17-hydroxycorticoid excretion

The progestational steroids are without effect on 17-hydroxycorticoid excretion but they cause a reduction in the excretion of 17-ketosteroids.

Other effects

Progestational steroids like progesterone promote desquamation of the superficial cells of the vagina and inhibit ferning of the cervical mucus.

Nor-ethisterone occasionally increases libido, but with prolonged therapy, sex drive may show a gradual decline With this compound patients gain weight and experience a feeling of well being

Relative activity

The relative activity of the progestational steroids is based on their ability to produce full secretory changes in the endometrium when given daily over 10–14 days in combination with oestrogen, following 14 days priming of the endometrium with oestrogen alone.

Allowing for the fact that some of the injected progesterone may be excreted as such before it is utilized, the above compounds are of approximately equal potency. They differ, however, in the duration of their action. In average doses (longer for larger doses) progesterone injections have an action for 2–3 days, 17α-hydroxy-progesterone caproate for 6–8 days, 17α-hydroxy-progesterone acetate for 6–8 days, and 17α-ethinyl-19-nor-testosterone enanthate for 13–17 days.

An implant of crystalline pressings of 100 milligrams progesterone produces therapeutic effects equivalent to 0·25 milligram of progesterone in oil given intramuscularly daily.

The other actions of the oral progestins do not always run parallel to the effect on the endometrium For example, nor-ethisterone is only half as active as its acetate ester in its action on the endometrium, but these two preparations are almost equivalent in their anabolic effect.

Parenteral administration

	Relative activity
Progesterone (20 mg injections daily for 10 days=200 mg.)	1 0
17 α-hydroxy-progesterone caproate (6×30 mg. injections=180 mg.)	1 0
17 α-hydroxy-progesterone acetate (6×30 mg. injections=180 mg)	1 0
17 α-ethinyl-19-nor-testosterone enanthate (1×150 mg. injection=150 mg)	1 0

Oral administration

	Relative activity
Progesterone	0 05
17 α-ethinyl-testosterone (ethisterone)	0 2
17 α-hydroxy-progesterone caproate	0 2
[illegible]	0 2
[illegible]	0 2
[illegible]	1 0
[illegible]	1 0
[illegible]	1 0
17 α-ethinyl-19-nor-testosterone acetate (nor-ethisterone acetate)	2 0
6 α-methyl-17-acetoxy-progesterone (Provera)	1 0
6 α-21-di-methyl-ethisterone (Dimethisterone)	1 0

Side-effects

In doses of 10–20 milligrams daily about 20 per cent of patients are intolerent to Enavid Nausea, general malaise, dizziness, breast discomfort and headaches are the symptoms most commonly experienced In some patients they are mild and soon wear off, especially if the steroid is taken at night, in others they are sufficiently severe to make continued treatment impossible

Nor-ethisterone (Norlutin) is well tolerated and side-effects are rare in the usual therapeutic dosage. However, with doses of 30 milligrams daily, nausea, bloating and headache may be experienced

Nor-ethisterone acetate is well tolerated even in high doses of up to 18 milligrams a day.

Withdrawal bleeding

Progesterone and 17α-hydroxy-progesterone caproate will only produce withdrawal bleeding if the endometrium has been primed with oestrogen. The nortestosterone compounds also require priming of the endometrium with oestrogens to produce withdrawal bleeding. Enavid contains 1·5 per cent of oestrogen and nor-ethisterone tablets usually also contain ethinyl oestradiol.

With progestational steroids given by mouth, withdrawal bleeding occurs about 3 days after cessation of treatment and lasts about the length of a normal period.

When progestational steroids are given by injection, the time of withdrawal bleeding depends on the duration of action of the compound and the dose administered. Withdrawal bleeding occurs 2–3 days after the injected steroid has ceased to have an effect on the endometrium.

With the long-acting parenterally administered steroids, withdrawal bleeding is occasionally prolonged for more than a week, and may be fairly heavy.

"Break through" bleeding

If, in a woman producing endogenous oestrogen, progesterone is given continuously from the time of ovulation, menstruation can be postponed for 15–30 days; but "break through" bleeding will then occur in spite of continued progesterone administration

With the nor-testosterone steroids "break through" bleeding does not occur so readily. It is least likely to occur with 17α-ethinyl-nor-testosterone (nor-ethisterone) and during the first cycle of 10 milligrams daily for 20 days it should not occur in more than 10 per cent of cases. With subsequent cycles the incidence of "break through" bleeding may fall to 6 per cent. It can be further reduced by increasing the daily dose to 30 milligrams or by giving oestrogen at the same time, but this increases the incidence of nausea However, this can be relieved by the administration of an antacid. Nor-ethisterone, if started as late as 7 days after ovulation, is still effective in delaying the onset of menstruation.

Arrest of anovular bleeding

The nor-testosterone steroids, in doses of 20 milligrams a day by mouth, usually arrest anovular bleeding in 12–48 hours. In one-third of patients treated for more than 14 days, recurrent scant bleeding may occur, but can be controlled by increasing the dose of nor-testosterone.

THE ENDOCRINE CONTROL OF NORMAL AND ABNORMAL UTERINE BLEEDING

Oestrogen withdrawal bleeding

In the surgically castrated woman, the a[illegible] ion of oestrogen, equivalent to 1 or 2 milligrams [illegible] ol daily, will st[illegible] liferation of the endometrium and on stopping t[illegible] n "withdraw[illegible] " occurs 7–10 days later.

Oestrogen "break through" bleeding

If oestrogen administration is continued, bleeding will be prevented for a variable period but sooner or later "break through" bleeding occurs This can be postponed by an increase in the dose of oestrogen.

Some varieties of menorrhagia and metrorrhagia, where no organic basis for the menstrual abnormality exists, are examples of oestrogen "break through" bleeding. This is especially true near the menopause when ovulation does not occur so consistently and an anovulatory cycle may terminate with oestrogen "break through" bleeding

Progesterone withdrawal bleeding

If, after oestrogen priming, progesterone is given by injection in doses of 20 milligrams daily for 3 or more days, progesterone "withdrawal bleeding" occurs 2–4 days after the progesterone is stopped.

Normal menstruation is thus an example of combined oestrogen and progesterone "withdrawal bleeding" after progesterone has been produced for long enough to stimulate full secretory changes in the endometrium.

Progesterone "break through" bleeding

If, against a background of oestrogen, progesterone is given daily by injection in 20 milligram doses, progesterone "break through" bleeding will occur between the sixteenth and twentieth days.

With continued progesterone production due to persistence of the corpus luteum, progesterone "break through" bleeding also occurs

Effect of high doses of progestational steroids

Sohval (1958) has been able to produce hypoplastic and atrophic endometrium by administering very large doses of 17α-hydroxy-progesterone caproate. Some cases of menorrhagia and metrorrhagia are associated with an atrophic or hypoplastic endometrium.

Enavid, which possesses oestrogenic as well as progestational properties, after administration for 2–3 weeks produces cytoplasmic enlargement of the stromal cells of the endometrium, but the uterine glands, after showing early secretory changes, regress to an early proliferative pattern Mixed types of endometrium are occasionally associated with menorrhagia and metrorrhagia.

Oestrogen concentrations associated with dysfunctional bleeding

Abnormal uterine bleeding without an organic basis may be associated with constant or fluctuating levels of oestrogen production and the histological pattern of the endometrium mirrors the concentration of circulating oestrogen (Fig 46)

Atrophic endometrium is associated with urinary oestrogen excretion of less than 10 micrograms of total oestrogen per 24 hours

Proliferative endometrium is found when the total urinary oestrogen excretion per day is between 10 and 30 micrograms and cystic glandular hyperplasia is common when the oestrogen concentration is above this level.

Uterine bleeding can occur while the oestrogen levels are rising, falling or remaining constant (Brown, Kellar and Matthew, 1959).

MANAGEMENT OF FUNCTIONAL UTERINE HAEMORRHAGE

Cases of menorrhagia or metrorrhagia without an organic basis are usually classified as examples of functional uterine haemorrhage.

The management of the individual case depends on:

(1) the patient's age,

(2) the degree of anaemia produced by the menstrual abnormality, and

(3) the degree of inconvenience and distress produced by the irregular or heavy menstrual loss.

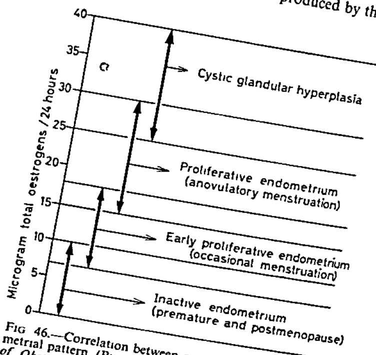


FIG 46.—Correlation between oestrogen levels and endometrial pattern (By courtesy of the Editor of *The Journal of Obstetrics and Gynaecology of the British Empire.*)

Curettage of the uterus at the time of examination under anaesthesia

The initial treatment should always be a thorough examination of the pelvic organs under anaesthesia and a curettage of the uterus with histological examination of the endometrium. If the time of the next period can be predicted from the history, the curettage is best performed a day or two before it is due. In addition to making a cervical smear at the time of the initial clinical examination, a biopsy of any suspicious area on the cervix is also made at the time of the examination under anaesthesia.

Only by investigations of this type can carcinoma be excluded and organic causes of menorrhagia and metrorrhagia such as polyps and small submucous fibroids be detected.

Subserous or intramural fibroids are frequently found in a patient with menorrhagia. However, the fibroids may be unrelated to the menstrual symptom (Sutherland, 1950). Menorrhagia due to fibroids and that resulting from hormonal disturbances can often be distinguished by the history Fibroids cause slowly progressive menorrhagia, the loss being heaviest on the second and third days, and although the periods gradually become heavier and longer, they usually remain quite regular until there is an interference with ovarian blood supply.

Munnell and Flick (1958) studied 464 patients suffering from this disorder and found, in two-thirds of the cases, normal proliferative or normal secretory endometrium Cystic glandular hyperplasia was present in 13 per cent and adenomatous hyperplasia in 3 per cent of their patients. Carey (1956), in a review of 148 cases of functional bleeding curetted at the National Women's Hospital, Auckland, in the premenstrual phase, found normal secretory endometrium in 50 per cent. This histological picture was encountered more frequently in the 25–40 years age group, while non-secretory endometrium was more common over the age of 40 years.

As well as being diagnostic and indicating the type of endometrium with which the menstrual abnormality is associated, curettage has a therapeutic value Munnell and Flick found it to be highly effective, particularly in the non-hyperplasia group, where it produced immediate cure in 87 per cent of cases In the presence of hyperplasia, however, recurrence of abnormal bleeding was common.

Adenomatous hyperplasia may be precancerous, consequently it should be treated by hysterectomy. As fertility is low in recurrent bleeding due to cystic glandular hyperplasia this condition is also an indication for hysterectomy

General measures

Iron administration

Iron preparations are given to allow regeneration of the blood that has been lost. Blood transfusion is to be avoided except in cases of emergency Even where surgery is indicated, the blood loss can usually be controlled by progestational steroids such as nor-ethisterone or nor-ethisterone acetate till the haemoglobin level is restored to normal In view of the effectiveness of these compounds, the risks and expense of blood transfusion are rarely warranted

Indications for endocrine therapy

When excessive menstrual loss is not controlled by curettage, endocrine therapy is indicated In the younger age groups this should be viewed as the main line of management, but in women over 35 years of age, who have completed their family, administration of hormones should be used as a temporary measure to obtain the optimum conditions for surgery.

Endocrine therapy of menstrual disorders

Arrest of a bleeding episode—endocrine haemostasis

Bleeding can be controlled by large doses of oestrogen by mouth, such as 10 milligrams of stilboestrol 4 hourly, but the patient invariably suffers from distressing nausea.

Greenblatt (1947) recommended 25 milligrams each of progesterone and testosterone propionate by injection daily for 4 days and Boschann (1958) found a single injection of 10 milligrams oestradiol benzoate combined with 125 milligrams 17α-hydroxy-progesterone caproate was effective in controlling bleeding in 24–48 hours, but withdrawal bleeding occurred 6 days later and continued for 7 days. A more convenient method of treatment is to give nor-ethisterone, 30 milligrams a day, or nor-ethisterone acetate, 10 milligrams a day, by mouth The nor-testosterone derivatives will control bleeding in 24–48 hours. Administration can be stopped after 26 days and withdrawal bleeding will occur 2–3 days later; alternatively nor-ethisterone acetate, 10 milligrams a day, can be continued till the haemoglobin concentration is back to normal. With higher doses, "break through" bleeding is less likely to occur. When these larger doses are employed nor-ethisterone acetate is tolerated better than nor-ethisterone or Enavid.

Management of metrorrhagia (acyclic bleeding)

If ovulation occurs in the subsequent cycle further therapy is usually not required The basal temperature or the vaginal smear can be employed to ascertain whether or not ovulation has taken place. If there is no evidence of progesterone secretion 10 milligrams of nor-ethisterone acetate daily can be administered for 6 days from the twentieth day of the cycle to produce a progesterone "withdrawal bleeding" about the time the period would be due.

A simpler system of management is to withhold treatment until the thirtieth day of the cycle. If vaginal bleeding has not occurred by then, the administration of 10 milligrams of nor-ethisterone acetate daily for 6 days will produce a progesterone "withdrawal bleeding" about the thirty-ninth day. If vaginal bleeding occurs before this and is heavier or longer than a normal period, the bleeding can be controlled with nor-ethisterone acetate administration, which then has to be continued until 3 days before the next withdrawal bleeding is required.

Menorrhagia (cyclical bleeding)

Nor-ethisterone acetate, 3 milligrams daily for 10 days from the fifteenth day of the cycle, will, in some cases, reduce the extent and duration of bleeding (Swyer, 1959).

Epimenorrhoea (polymenorrhoea) and epimenorrhagia

Administration of nor-ethisterone acetate is started 5 days before the expected date of the next period. Bleeding will occur about 3 days after the treatment is stopped.

Supervoltage therapy

With poor operative risks over 40 years of age endocrine control of functional uterine haemorrhage persisting after curettage can be continued as long as necessary or the onset of the menopause can be accelerated by supervoltage irradiation of the ovaries In the past, obese patients were treated with intra-uterine radium in preference to deep x-ray irradiation of the ovaries. With supervoltage this expedient is no longer necessary as, even with obese patients, an adequate dose of *gamma* radiation can be delivered to the ovaries without excessive absorption by the more superficial tissues.

Surgery

Surgery is normally preferred to *gamma* radiation as in this way ovarian function can be conserved. In view of the effect of the sex steroids on lipoid metabolism, they may be of value in reducing the risk of coronary thrombosis as well as making menopausal adjustments easier.

Abdominal versus vaginal hysterectomy

Abdominal and vaginal hysterectomy both have their enthusiastic supporters. When a woman who requires a hysterectomy is also suffering from some form of prolapse or stress incontinence then vaginal hysterectomy offers the opportunity of correcting both abnormalities during the one operative procedure If the uterus is enlarged, or there is little descent when traction is placed on the cervix, vaginal hysterectomy may be technically difficult

Abdominal hysterectomy has the advantage of better exposure of the pelvic organs and adhesions, and pathological conditions of the ovary can be handled more satisfactorily. If care is taken with haemostasis and the bowel is packed away and not handled more than necessary, and the temptation to remove a normal appendix is resisted, post-operative morbidity is often less with abdominal than with vaginal hysterectomy. Even when there is some degree of uterine descent, the top of the vagina can be given adequate support, if, when carrying out a total abdominal hysterectomy, the lateral cervical ligaments are sutured to the vaginal vault, and to each other

With vaginal hysterectomy post-operative catheterization is required for a longer period and this leads to a higher incidence of morbidity. Backer and Kristoffersen (1957) found that vaginal hysterectomy did not possess any primary advantage over the abdominal procedure, but recurrence of prolapse recurred in half the cases treated by vaginal hysterectomy Hawksworth and Roux (1958) claimed to prevent the development of enterocele following vaginal hysterectomy by carrying out a high fascial repair above the level of the levatores ani

Normally there is little place for subtotal hysterectomy. As 1·5 per cent of women eventually develop carcinoma of the cervix (Carey and Gardiner, 1959), this risk is removed by total hysterectomy If the cervix is infected or abnormal in any way it should be removed In nulliparous women with no abnormality of the cervix, who can be trusted to have a cervical smear taken every 2 years, a small stump of cervix can be left if it is important to avoid any shortening of the vagina Occasionally this may be desirable in a woman who has been recently married.

TREATMENT OF DYSMENORRHOEA

Agents which inhibit ovulation are usually successful in relieving primary dysmenorrhoea Stilboestrol, 1 milligram twice a day from the second to the twenty-first day of the cycle, is effective in this regard Nor-ethisterone, 10 milligrams given twice a day from the fifth to the twenty-fifth days of the cycle, is an effective alternative in those cases in whom nausea or break-through bleeding occurs while taking stilboestrol.

AMENORRHOEA

If for diagnostic or psychological reasons cyclical bleeding from a secret- endometrium is required in women suffering from amenorrhoea, oral nor-eth terone acetate can be employed as an alternative to parenteral progesterone

If the endometrium is atropic, indicating that little endogenous oestrogen being formed, stilboestrol, 1 milligram twice a day, is given for 24 days and nor ethisterone, 6 milligrams twice a day, is prescribed from the fifteenth to the twenty-fifth days.

If the endometrium shows development similar to that found in the late follicular phase, then nor-ethisterone acetate, 6 milligrams twice a day for 10 days, will usually produce a withdrawal bleeding about 3 days after the last dose has been taken.

PROGESTINS DURING PREGNANCY

Knaus (1934) claimed that progesterone had an inhibitory effect on the myometrium. In spite of the fact that Henry (1950) was unable to reproduce the results of Knaus, progesterone has been used for treating threatened and habitual abortion, and following surgical procedures undertaken during the first and second trimesters, it has been administered in the hope of reducing the risk of miscarriage

In both pigs and sheep, but not in rats, progesterone has an adverse effect on the survival of the embryos, and because of marked species differences, it is likely to be misleading to apply the findings in rabbits or other animals to man.

Goldzieher (1958) reviewed the published data on habitual abortion and found that, in a woman who had never had a term pregnancy, the risk of abortion in the pregnancy following two or three previous abortions, was only 24 per cent, and after four previous abortions, was 40 per cent. None of the results reported in the literature to date indicate that progesterone therapy in habitual or threatened abortion is any better than psychotherapy alone However, Boschann (1958) ascribed this to the small doses of progesterone that were used in most of the investigations reported in the literature. He recommended treatment of both threatened and habitual aborters with high doses of progesterone. To reduce the number of injections, 250 milligrams of 17α-hydroxy-progesterone caproate, which is weight for weight as active as progesterone, was given twice weekly. A single injection of this preparation is slowly absorbed over a week, but to overcome the latency in effect of the depot preparation, 50 milligrams of progesterone in oil was given intramuscularly at the same time as the initial injection of 17α-hydroxy-progesterone caproate. In spite of these high doses of progesterone, the Boschann salvage rate of 67 per cent in habitual abortion was no higher than the spontaneous cure rate of 75 per cent, which can be expected without any special treatment.

Nor-ethisterone has been used as a substitute for progesterone in the treatment of habitual or threatened abortion However, its use during pregnancy, in high doses, for long periods, has been associated with androgenic effects and for this reason it must be employed with care. If for psychological reasons a progesterone

preparation is to be employed, it is better to give 17α-hydroxy-progesterone caproate An implant of 100 milligrams of crystalline progesterone liberates 0·25 milligram of progesterone daily and so would have only a homeopathic effect

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ABSTRACTS RELATING TO GYNAECOLOGY AND OBSTETRICS

Carcinoma of the cervix uteri

Irradiation sensitivity

In an ... of cervical carcinoma in human be ... ue culture malignant epithelium ob ... hantom. The success in growing hu ... leal on the number of explants cultivated per tube. When larger quantities of tissue were cultivated, viable tumour fragments grew more readily Outgrowth usually occurred within 2 days but a few did not produce tumour cells till the fourteenth day. Since, in most cases, the fibroblasts did not appear until the twelfth to the fourteenth day of cultivation, the carcinoma cells grew out and became well established before the fibroblasts made their appearance. In

a few instances, where the epithelial cells appeared late, an extensive reticulum of fibroblasts appeared in 4–5 days, but were later pushed away by the compact epithelial sheet of carcinoma cells. On the other hand, late growing fibroblasts in some cases appeared to be extremely aggressive, rapidly infiltrating, outgrowing and finally destroying the carcinoma sheet. Different types of epithelial outgrowths were observed. In some instances only compact sheets of cells would emerge, while in others, individual loose epithelial cells appeared. The adenocarcinomas of the cervix were indistinguishable from the squamous cell carcinomas during the first 4 days of cultivation. Thereafter the cells usually differentiated to form the typical glandlike spaces seen in histological sections of these tumours The criterion selected for the end point of irradiation effect was the destruction of all outgrowing tumour cells. Some cultures ceased growing after partial irradiation only to manifest regrowth some weeks later. For this reason all cultures were maintained for at least 1 month after all growth had ceased. On the basis of the growth response to irradiation, it was possible to classify cultures into those resistant, intermediate and sensitive to deep x-ray therapy. The correlation between the *in vitro* observations and the clinical response of the patient to treatment has still to be completed. The tissue culture technique gives no indication of host resistance to the carcinoma

Transperitoneal pelvic lymphadenectomy following supervoltage irradiation

RUTLEDGE and FLETCHER (1958) discuss 100 Stage III cases of carcinoma of the cerv treated by supervoltage irradiation from a 22 mega-electronvolt betatron and by insertic of radium into the uterus and upper vagina. A total tumour dose of 6,000 rontgens wa delivered to the whole pelvis in 6 weeks from the betatron, using anterior, posterior anc two lateral portals The dose received by the hypogastric and external iliac lymph nodes from the radium source varied from 300 to 500 rontgens From a study of carcinoma of the head and neck it had been found that, following irradiation, up to 3 months was necessary for tumour cells to disintegrate, consequently transperitoneal pelvic lymphadenectomy was performed 3 months after irradiation. Positive nodes were found within the irradiated field in 5 cases, outside the irradiated field in 8 patients and both inside and outside the area irradiated in 9 of the cases. From a study of the literature, the number of cases of Stage III carcinoma of the cervix expected to have positive lymph nodes prior to irradiation was estimated to be at least 50 per cent. Consequently supervoltage treatment of the pelvis had reduced the incidence of lymph node involvement by more than 50 per cent.

Carcinoma of corpus uteri

Vaginal metastases

Vaginal metastases from adenocarcinoma of the corpus uteri were studied by RUTLEDGE, SO KLIM TAN and FLETCHER (1958) A 10 per cent incidence of vaginal metastases has been reported following total hysterectomy as the sole method of treating adenocarcinoma of the corpus of the uterus. In 95 cases treated in Houston, Texas, by intra-uterine and vaginal radium prior to hysterectomy, the incidence of vaginal metastases was only 1 5 per cent.

Threatened abortion

Ambulation

In patients threatening to miscarry, a comparison was drawn by DIDDLE and O'CONNOR (1958) between those permitted a reasonable amount of activity and those confined to bed The incidence of inevitable abortion in the two groups was the same.

Carpal tunnel syndrome in pregnancy

LAYTON (1958) investigated acroparaesthesia in pregnancy and the carpal tunnel syndrome. The carpal tunnel syndrome is caused by compression of the median nerve in the carpal tunnel below the flexor retinaculum. This syndrome shows a definite tendency to be

swelling and stiffness of the hand and fingers and associated clumsiness may be reported In mild cases symptoms are often only noticed on awakening, but severe cases may cause considerable loss of sleep. In nearly all cases improvement occurs with the use of the hands during the day. The carpal tunnel syndrome must be differentiated from: (a) spondylosis and cervical disc lesion—a nerve root is involved in this condition and the distribution is not that of the median nerve; (b) thoracic outlet syndrome—this is usually

Cervix uteri

Distribution of squamous and columnar epithelium

The distribution of squamous and columnar epithelium in the cervix in relation to the external os at different periods of life was studied by SCHNEPPENHEIM and his colleagues (1958) by the histological examination of 853 uteri, 258 of which were collected from post-mortem examinations and 595 from hysterectomies In children squamous epithelium frequently penetrated into the cervical canal. The cervical glands only rarely reached down as far as the level of the external os During the reproductive period the cervical glands frequently extended on to the portio vaginalis After the menopause the cervical glands were again restricted to the cervical canal, and the older the woman, the greater the tendency for the squamous epithelium to grow into the cervical canal The squamous

al carcinoma did not always site of junction of these two oestrogen secretion

Ovarian activity following hysterectomy

Ovarian function following hysterectomy was studied by WHITELAW (1958) by means

estimations demonstrated that the oestrogenic activity of ovaries conserved at hysterectomy persisted for years. There was no indication that hysterectomy hastened the onset of the menopause A study of the basal temperature records and pregnanediol estimations indicated that the incidence of ovulation and corpus luteum formation was comparable in those women who had had their ovaries conserved at the time of hysterectomy and in those who had not been subjected to any surgical procedure Although symptoms usually associated with the menopause were found to be more prevalent among the castrated subjects than among those who had undergone hysterectomy with conservation of one or both ovaries, such symptoms were found to be an unreliable indicator of the state of the ovarian activity of the individual. The application of the stumps of the round and broad ligaments to the vaginal vault had no adverse effect on the continuation of ovarian activity.

Stein-Leventhal syndrome

The Stein-Leventhal syndrome is described by LEVENTHAL (1958) The syndrome is characterized by secondary amenorrhoea, sterility, hirsutism and polycystic ovaries Secondary amenorrhoea the amenorrhoea may be absolute or may be interrupted by occasional periods of anovulatory bleeding. Sterility about 2 per cent of infertile patients

suffer from this syndrome. Hirsutism: hirsutism occurs in approximately 50 per cent of the patients. When present it may be very mild or very extensive. The urinary excretion of 17 ketosteroids is normal. Polycystic ovaries: the demonstration of bilateral polycystic ovaries is the keystone in the diagnosis. In cases of doubt examination under anaesthesia, culdoscopy (inspection of the pelvic organs through the pouch of Douglas) or pneumo-roentgenography may be required to evaluate the size of the ovaries. As regards the pathology, the ovaries are enlarged to a size approaching that of the body of the uterus. The tunica is thick, tough and pearly white. Cut sections reveal a thick fibrous capsule surrounding a stroma containing innumerable follicle cysts filled with clear fluid. Hyper-plasia of the theca interna cells is a very consistent finding, and corpora lutea are characteristically absent. The endometrium usually shows proliferative changes only. Occasionally it may be hyperplastic or atrophic. In a few cases secretory changes may be present but in these circumstances the ovaries show luteinization of the theca interna cells but no evidence of corpus luteum formation. Ingersoll reported normal urinary follicle-stimulating hormone excretion in 26 patients with the Stein-Leventhal syndrome. In the differential diagnosis the following conditions are to be considered: masculinizing tumours of the ovary, such as arrhenoblastoma, hilus cell tumour and adrenal rest tumour, although producing secondary amenorrhoea and hirsutism without elevation of 17 ketosteroids, are rare and unilateral and are usually associated with other signs of virilism rather than just hirsutism. In adrenal hyperplasia administration of cortisone or one of its derivatives results in the re-establishment of normal menstruation, but this type of steroid therapy is ineffectual in treating the secondary amenorrhoea associated with the Stein-Leventhal syndrome. With adrenal tumours producing hirsutism and amenorrhoea, there is no response to administered cortisone or similar compounds but the 17 ketosteroid excretion is high. In regard to treatment true cases of the Stein-Leventhal syndrome respond to wedge resection of the polycystic ovaries. Following this treatment normal menstrual function returned in 95 per cent of cases and in 88 per cent infertility was relieved.

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THE NATURAL HISTORY OF BREAST CANCER

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EPIDEMIOLOGY

At the present time in England and Wales there are at least 25,000 women suffering from breast cancer and the incidence of the disease has been rising for 30 years because the proportion of women over the age of 60 years in our population has been steadily increasing

In considering the natural history of breast cancer the relevant evidence is of two kinds:

(1) *Epidemiological.*—The frequency of occurrence of the disease in populations; the estimation of morbidity and mortality rates, the correlation of statistical evidence with those intrinsic and extrinsic factors which may be related to causation, susceptibility and the clinical course of the disease

(2) *Clinical and pathological.*—The study of the onset, clinical course and duration of the disease, the correlation of this clinical information with evidence provided by clinical and experimental endocrinology, and with the morbid anatomy and histology of the tumour, its local extensions and its distant metastases.

Definition of "breast cancer"

It is first essential to define what we mean by "breast cancer". Mammary sarcoma, for instance, may be included in one series of cases or omitted from another and, in any event, many of the "breast cancers" included in statistical surveys involving large numbers have not been submitted to histological examination. Although this is unlikely to have any significant effect on statistics, the inclusion of tumours arising in the connective tissue of the breast may account for the cases reported as "prepubertal breast cancer" and thus for the false

deduction that carcinoma of the breast can arise before ovarian function is established.

There are two dissimilar varieties of breast cancer. The first, and the more lethal, is spheroidal-cell carcinoma with an abundant fibrous stroma (scirrhous cancer), far and away the most common of all malignant mammary tumours It pursues an inexorable course with relatively early widespread blood-borne metastases. The second variety of cancer, almost always included in records, is papillary carcinoma, or "duct cancer", whose papillary structure is usually clearly discernible and whose origin from innocent papillomatosis of the breast ducts, down to but not including the breast lobules, is not in question. Duct cancer is

TABLE I

AGE STRUCTURE OF POPULATIONS

Country	*Percentage of population over 60 years of age*		*Variation in a 50 years' period*	
	About 1900	*About* 1949	*Increase*	*Decrease*
England and Wales	7·5	15·9	8·4	
New Zealand	6·8	13·7	6·9	
Australia	6·2	12·5	6·3	
U.S.A.	6·4	11·6	5·2	
Germany	7·8	12·9	5·1	
Switzerland	9·3	13·8	4·5	
Republic of Ireland	10·7	14·6	3·9	
France	12·4	16·3	3·9	
Denmark	9·9	13·1	3·2	
Norway	10·9	13·5	2·6	
Finland	8·2	10·8	2·6	
Italy	9·6	11·8	2·2	
Portugal	9·6	9·9	0·3	
Chile	6·4	5·9		0·5
Japan	8·2	7·6		0·6

infiltrative and destructive. Radical mastectomy is essential for its treatment and frequently effects a permanent cure. Blood-borne metastases, if they occur, tend to be long delayed and limited in extent

There is no question that the overriding lethal factor in breast cancer is the occurrence of blood-borne metastases to vital organs or surgically inaccessible tissues, the inclusion of duct cancer with scirrhous cancer in statistics relating to morbidity, mortality, and more especially to the effects of treatment, introduces a serious error, the magnitude of which is to some extent offset by the fact that for one "duct cancer" approximately four "scirrhous cancers" are likely to be encountered.

It is quite clear that the solution of the many unsolved problems relating to breast cancer would be greatly assisted if it were possible to establish compulsory notification of the disease. At the present time Norway is the only country in which such notification is in operation.

FREQUENCY OF OCCURRENCE

Rise in frequency

During the last half-century there has been a progressive and almost world-wide increase in the frequency of occurrence of breast cancer in the very large majority of countries where medical services are able to compile reliable statistics. The increases in morbidity and mortality rates are almost entirely accounted for by the phenomenal increase in the numbers of adults over the age of 60 years in those countries in which a significant increase has been observed

Age structure of populations

In 1900, 7·5 per cent of the population of England and Wales were over 60 years of age; in 1949 this percentage had risen to 15 9. Table I shows the extent to which the age structure of the population has altered in 15 countries over a period of approximately 50 years

MORTALITY RATE IN FEMALE BREAST CANCER

The Registrar-General (1957) gave the information included in Table II

TABLE II

	Year under review		
	1955	1956	1957
Total female deaths (all causes)	251,888	253,427	248,463
Deaths from malignant disease	44,097	44,679	44,853
Percentage of deaths from malignant disease	17 5	17 62	18 05
Breast cancer accounted for:			
Number of deaths	8,495	8,580	8,613
Percentage of total deaths	3·37	3 38	3 46
Percentage of deaths from malignant disease	19 264	19 203	19 202

When corrected for the change in the age structure of the population, "Breast cancer death rates in England and Wales have varied little during 30 years, except that the rates have tended to rise slightly at ages under 45" (Stocks, 1957). Studies by Stocks in which the mortality rates of "cohorts" of women born about 1870 and at intervals to 1905 were analysed show "how slight on the whole the change has been". This survey includes the period 1885–1935 during which there was a marked fall in fertility in women Stocks pointed out that this should have induced a considerable rise in death rates after 45 years of age. In the absence of this expected increase it is likely that there has been a compensatory improvement in survival rates (Stocks, 1953)

Geographical distribution

In a recent report by the World Health Organization (1957) the mortality rates of breast cancer in eight countries have been assembled and are shown in Table III.

The similarity in death rates between the ages of 35 and 60 years for the first five countries is remarkable. Denmark, however, has higher rates after the age of 60 years. In Italy and Finland the rates are significantly lower throughout. The extremely low mortality in Japan in comparison with other countries is outstanding and has considerable significance in any study of the natural history of breast cancer provided that the standard of medical diagnosis and death certification can be guaranteed. Stocks (1957) was satisfied that the Japanese figures are statistically acceptable. He pointed out that the total cancer death rates for women in Japan are only slightly below those for England and Wales, that the standardized death rates for gastric and uterine cancer are double those in England and Wales, and that the low risk from breast cancer is being compensated up to the age of 60 years by the higher risk from uterine cancer (Stocks, 1956). The relationship between the low risk from breast cancer and the total duration of lactation during the whole of the reproductive life of Japanese women is discussed in a later section.

TABLE III

MEAN ANNUAL DEATH RATES FROM BREAST CANCER PER 100,000 WOMEN IN 1952–1954

Age group (years)	*England and Wales*	*Denmark*	*Canada*	*New Zealand*	*U.S.A.*	*Finland*	*Italy*	*Japan*
25—	1	0 5	2	1	2	0·4	1	0 5
30—	5	4	6	4	6	3	3	2
35—	14	13	16	12	14	7	10	4
40—	30	25	29	25	27	13	17	7
45—	46	42	48	48	42	24	26	9
50—	56	58	51	61	54	31	33	11
55—	71	66	68	70	65	35	41	13
60—	84	92	82	72	76	42	46	13
65—	101	113	96	80	88	51	50	13
70—	118	138	113	102	104	41	66	14
75—	143	178	137	147	132	62	82	16
80—	177	199	157	186	157	62	95	17
85 & over	227	324	236	265	186	38	109	

GENERAL SUSCEPTIBILITY

Marital history

A greater liability for single women in Italy to develop breast cancer was demonstrated by Stern in 1842. The Registrar-General (1923) gave the incidence of breast cancer for England and Wales, as shown in Table IV (quoted by Stocks, 1957).

The excess mortality in single women was found at each age after 35 years by Lane-Claypon (1926).

Peller (1940), from the records of the Vienna University Clinics, compiled the data given in Table V.

Stocks (1939) for England and Wales, Dorn (1943) from Australian data, Clemmesen (1951) for Denmark, and Denoix (1954) using French records, have

TABLE IV

Period	*Breast cancer mortality (standardized rate per million)*	
	Single	*Married and widowed*
1911–1920	343	238

found the same inverse relationship between breast cancer rate and child-bearing.

In more recent studies of data from England and Wales furnished by the Registrar-General, Stocks (1955) has produced statistical evidence showing that

(1) There is no difference in the mortality rate from breast cancer between single and infertile [illegible]

[illegible]

for this difference

Stocks (1957) has also investigated the age at marriage and the numbers of confinements in 421 women aged 42–71 years living in Merseyside and detailed

TABLE V

Total women over 45 years having cancer, all sites	*Percentage incidence of breast cancer*	
	In childless women	*In women having 8 or more children*
2927	18	8

In this series there was no significant difference in the percentage incidence of gastric and intestinal cancer between the fertile and infertile groups

analyses suggest that "a dearth of confinements during the first 10 years or so of the reproductive period increases the risk of breast cancer developing after 45". Delay in marriage increases the risk presumably because the total period of lactation is significantly curtailed

Lactation

The high birth rate in Japan does not account for the extremely low incidence of breast cancer in Japanese women The true explanation lies in the fact that breast feeding in Japan is customarily prolonged over periods up to 3 years. Table VI gives relevant figures compiled by Segi (1955).

TABLE VI

Total women without cancer	*Average lactation period*	*Percentage of breast-fed children*
4180	18 9 months	85 per cent

When Japanese women over the age of 40 years living in rural areas and suffering from breast cancer are compared with cancer-free controls of comparable age, contrasts emerge, as shown in Table VII.

TABLE VII

Average number of children		*Average lactation period per child (in months)*		*Total months of lactation*	
Women with breast cancer	Controls	Women with breast cancer	Controls	Women with breast cancer	Controls
3·4	5·0	16·86	18·6	55	90

In the cancer-free group, therefore, the average number of children is 1·6 more the average period of lactation per child is 1·74 months longer; the total duration of lactation over the whole reproductive period is 35 months longer than in women with breast cancer.

Comparison of the relationship between breast cancer and lactation in Great Britain and Japan is given in Table VIII.

TABLE VIII

	Japan	*Great Britain*	*Ratio*
Approximate total period of lactation	7½ years	1½ years	5 : 1
Death rates from breast cancer per 100,000 women	138	1073	1 : 7·7

The mortality rate of breast cancer in Japan—less than one-fifth of the rate in Great Britain—is clearly associated with the fact that the total period of lactation in Japanese women is five times longer than the total period in Great Britain.

Correlation of Incidence of Breast Cancer with Age at Apparent Onset

The first relevant symptom noticed by the patient which prompts her to consult her doctor and leads to a diagnosis may be described as the "reputed" or "apparent" onset of the disease. The date of this occurrence must be taken as the only available indication of the onset of the disease for statistical and clinical purposes *It provides little or no evidence of the true onset, which must be a matter for conjecture* Many believe that when the tumour becomes palpable by the patient it is already "old".

There have been extremely few, if any, authentic cases of mammary cancer reported in the prepubertal period before the ovary is capable of responding to pituitary gonadotrophin. An onset under the age of 20 years is very rare and the incidence of cases arising below 25 years is about 0·02 per cent. There is a lag period of about 15 years from the age of 25 years onwards before any appreciable number of cases arises. This lag-phase may eventually prove to be a "period of

incubation". It is succeeded by a sharp rise of incidence to a maximum at about 50 years of age. Incidence is then quite sharply reduced to a "bumpy" but slowly rising plateau of inconstant configuration which terminates in the period of maximum incidence at about 62 years (Fig. 47). It then bends abruptly downwards to a sharp fall which is clearly due to the elimination of potential cases by other diseases

The mean age at apparent onset varies with the structure of the population studied If composed of patients coming to hospital for treatment, many of them being operable, the mean age lies at about 50 years. If a series contains a significant number of patients whose disease has progressed because of delay in seeking advice, the mean age rises—as in the series reported by Harnett (1952); his mean figures are given in Table IX.

TABLE IX

	Single women	*Married and widowed*	*Total*
Number of cases	471	1658	2129
Mean age	55 6±0 6	57 4±0·3	57·0±0 4
Standard deviation	12 8±0 4	12·5±0·2	12·6±0 2

Other estimations of the mean age in years at apparent onset are:

Greenwood (1926)	57
Nathanson and Welch (1936)	58
Wade (1946)	56 72
Simmons and Daland (1900)	50 3
Deaver and McFarland (1917)	50 1

The bimodal distribution

When correlating the incidence of breast cancer with the age of onset it has been customary to plot incidence against age over 10-year periods. Such records show a unimodal distribution with a plateau of irregular configuration extending from the age of 50 years, rising to a maximum incidence at 65 years

When incidence in a large series of cases is plotted against age intervals of 5 years, the curve shows a bimodal distribution reaching the first peak at 45–49 years, followed by a striking and abrupt fall in incidence from 50 to 54 years, and rising to a second peak at 55–65 years, the latter peak being broader than the first.

Anderson and his colleagues (1950) combined the impressive records of the Danish Cancer Registry with records compiled in Great Britain and in the U.S A.

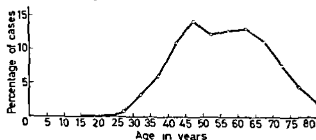


FIG 47 —Bimodal distribution of breast cancer according to age at onset—10,117 cases—data shown in Table X (Reproduced by courtesy of the Editor of *Cancer*.)

Their results (Fig. 47 and Table X) are based on the age records of 10,117 cases from these three widely separated countries.

TABLE X

BIMODAL DISTRIBUTION OF CASES OF BREAST CANCER ACCORDING TO AGE AT ONSET (ANDERSON AND HIS COLLEAGUES, 1950)

Age at onset (years)	*Danish Registry (Jacobsen)*	*Britain*		*U.S.A. Conn. Registry (Griswold)*	*Anderson and his colleagues*	*Total*
		Penrose and his colleagues	*Harnett*			
Up to 24	3	1	4	27	0	35
25—29	8	5	(13)	63	3	92
30—34	69	21	(46)	178	10	324
35—39	87	43	122	348	26	626
40—44	175	70	202	628	40	1,115
45—49	262	102	278	735	45	1,422
50—54	172	71	294	661	38	1,236
55—59	204	60	272	730	42	1,308
60—64	223	64	280	719	31	1,317
65—69	171	37	265	633	38	1,144
70—74	115	24	185	448	25	797
75—79	48	10	117	275	13	463
80 and over	28	2	51	150	7	[illegible]
Total	1,565	510	2,129	5,595	318	10,117
Mean age at onset	55·0	51·7	57·0	56·0	55·1	
Standard deviation (years)	12·06	11·4	12·6	13·0	12·8	
Standard error in years	0·31	0·50	0·27	0·17	0·72	

Fig. 48 shows a curve of similar configuration based on the records of breast cancer patients admitted to the Memorial Hospital, New York.

An almost identical fall in the prevalence (this is expressed as the number of patients known to have cancer during a year per 100,000 population) of breast cancer during the ages of 50–54 years was demonstrated by Clemmesen (1951); his results are shown in Fig. 49.

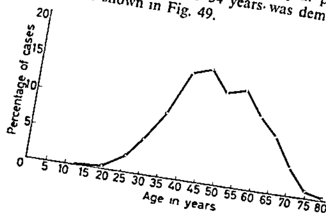


FIG. 48.—Bimodal distribution of 13,054 cases of breast cancer according to age at onset, seen at the Memorial Hospital, New York. (Data kindly supplied by Dr. N. E. Treves.)

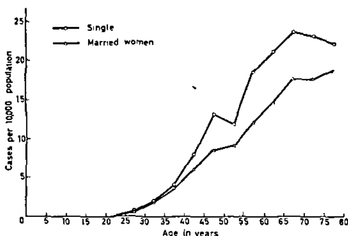


FIG. 49—Prevalence of breast cancer in Denmark plotted in 5-year age groups. (From data compiled by Clemmesen, 1951, from the *Danish Cancer Registry*, 1943–47)

Tumour regression at the menopause

It is, in all probability, significant that the conspicuous period of low incidence corresponds to the duration of the normal menopause, and it is tempting to assume that this period of physiological castration is unfavourable to the development of breast cancer because it corresponds to a period during which oestrogen production progressively falls The second peak may be associated with the re-establishment of oestrogen production by the adrenal cortex.

These assumptions are greatly strengthened by the observation that women who develop breast cancer a few years before the menopause and enter the menopause when their tumours have metastasized, show a strong tendency to a natural and significant objective growth regression which persists through the menopausal years, *to be succeeded invariably by a period of growth progression which can*, however, be halted by surgical adrenalectomy Hadfield and Holt (1956) have published eleven cases which illustrate this naturally occurring phenomenon (Table XI)

TABLE XI

ELEVEN CASES OF METASTASIZING PREMENOPAUSAL BREAST CANCER SHOWING A NATURAL GROWTH REGRESSION STARTING DURING THE MENOPAUSE (HADFIELD AND HOLT, 1956)

Premenopausal *duration of the disease in months*	Menopausal and postmenopausal *duration of growth regression in months*
10	30
12+	13
11	12
108	42
24	15
42	3
12	19
3	15
120	9
72	24
120	48

In interpreting these results, due allowance must be made for the fact that natural growth regressions during the menopause can be expected to occur only in the 50 per cent or so of all breast cancer patients whose growths are hormone-dependent. During the period of the investigation reported above, other cases of premenopausal breast cancer were encountered in which there was no objective growth regression during the menopause. Hadfield and Holt also compared the duration of the natural regression during the menopausal years with the duration of regressions induced by ovariectomy The period was significantly shorter in the ovariectomy group, suggesting that an additional factor, possibly a pituitary hormone, was concerned in the natural menopause. They also found in the cases of natural menopausal growth regression that when tumour growth again became progressive this could be halted by bilateral adrenalectomy.

THE DURATION OF LIFE IN UNTREATED BREAST CANCER

The objective in the treatment of breast cancer may be either permanent cure or prolongation of life, depending upon the overriding lethal factor of blood-borne metastatic spread.

Any claim that a certain form of therapy has effected a cure or prolonged life cannot be accepted unless an adequate number of accurately recorded therapeutic results is subjected to impartial, rigid and skilled comparison with the natural history of the disease in a statistically significant number of unselected and untreated cases.

It is becoming increasingly difficult to study large populations of untreated breast cancer patients. Skilled treatment and diagnostic accuracy are now widely available in many countries and the untreated cases belong to small, carefully selected groups in [illegible]

For this reason t [illegible] of untreated cancer a [illegible] The most comprehensive and reliable of these studies was made by Greenwood (1926), a pioneer medical statistician, assisted by a team of skilled clinical observers and pathologists, who analysed the duration of life in untreated cancer of the breast, rectum, cervix uteri, oral cavity, stomach, larynx and oesophagus. Some of their results are shown in Table XII.

TABLE XII

DURATION OF LIFE IN UNTREATED CANCER MEASURED FROM THE CLINICAL (APPARENT) ONSET—DATA OF GREENWOOD (1926)

Site	Total No of cases	Mean age at onset (in years)	Mean duration (in months)	Standard deviation	Probable error of means	Death of 50% cases (months)	Death of 75% cases (months)
Breast	651	57	38	43	1 2	26	46
Rectum*	887	55	27	25	0 6	22	34
Cervix uteri	1 749	48	21	17	0 3	17	24
Larynx	129	52	15	11	0 7	11	16
Oesophagus	299	55	12	11	0 4	7	14

* Palliative colostomy was carried out in rectal cancer cases

The mean duration of life in untreated breast cancer from its apparent onset varies from 30 to 40 months It is raised when a series of published cases contains

a disproportionately large number of patients surviving for 5 years, or by the chance inclusion in a series of a relatively small number of patients surviving for 10 or more years It is lowered when a disproportionately large number of patients fails to discover a mass in the breast until the disease is well advanced. In any event, it will be raised or lowered if the proportion of duct cancers to the more lethal scirrhous cancers is higher or lower than the average. A mean figure, possibly approximating to the truth, was obtained by taking the mean of the means of those published series of untreated cases in which the numbers of patients recorded were large. Such an estimate gave a mean duration of 38 months.

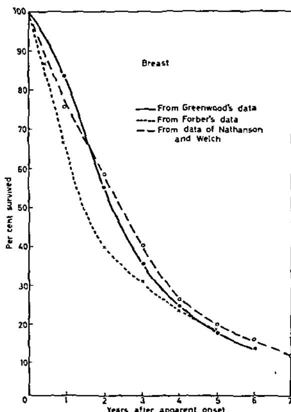


Fig. 50—The duration of life in untreated breast cancer. The vertical lines show the standard error of the mean survival at each age period. (After Shimkin, 1951, reproduced by courtesy of the Editor of *Cancer*.)

The data shown in Table XII provides valuable information on the relative malignancy of some common forms of untreated cancer, as judged by the mean duration of life and the mean periods elapsing until one-half and three-quarters respectively of the cases had died. Both estimates for untreated breast cancer are significantly higher than for any of the other varieties of untreated cancer in the series, strongly suggesting that breast cancer is the "slowest killer". It must be emphasized that this conclusion applies to the average behaviour of a population, and in view of the remarkable individual variations in survival in this disease it would obviously be fallacious to place much weight on this "group characteristic" in the prognosis of the individual case.

Loss of the normal expectation of life

Wade (1946) has calculated the number of years of life lost from untreated breast cancer according to the age at death, as follows:

Age at death (years)	*Years of life lost*
25—34	38·44
35—44	28·96
45—54	21·01
55—64	13·23
65—74	6·56
75 and over	2·76

The duration of life in untreated breast cancer has been presented in graphic form by Shimkin (1951). The superimposed curves shown in Fig. 50 were obtained by plotting the percentage of survivors against time in years. Greenwood (1926) compiled data based on a total of 651 untreated cases observed in London hospitals and occurring between 1882 and 1924. Data compiled by Forber (1931) were based on 64 untreated cases observed in London; a significant proportion did not die in hospital. The case records studied by Nathanson and Welch (1936) were observed between 1912 and 1935 in two hospitals in Massachusetts which dealt with one-fifth of all cancer in the State. The combined results cover a period of 53 years and deal with widely scattered populations. They show remarkable agreement and demonstrate that approximately 20 per cent of untreated breast cancer patients are alive 5 years after the onset of symptoms.

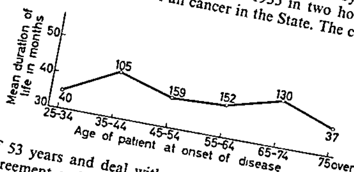


FIG. 51.—Mean duration of life in untreated breast cancer according to age at reputed onset. Numbers at the points indicate the cases (Greenwood's data, 1926; adapted by Shimkin, 1951; reproduced by courtesy of the Editor of *Cancer*)

In spite of many expressed opinions to the contrary, Greenwood's figures show no significant or consistent increase or decrease in the mean life span of untreated breast cancer when cases are grouped according to the age of onset (Fig. 51).

NUTRITION AND THE GENESIS OF BREAST CANCER

The progress of breast cancer is slow in the senile and under-nourished patient suffering from an atrophic scirrhous growth, rapidly growing tumours are often seen in over-nourished women. Beyond this there is little relevant evidence concerning the rate of growth of breast cancer with the nutritional state, nor is there any information on the relation between the susceptibility to develop cancer in over-nourished women as compared with the under-nourished

Experimental evidence is now available, however, which relates the state of nutrition to the genesis of cancer in the experimental animal (Tannenbaum and Silverstone, 1957). From the results of a long series of carefully designed experiments these workers conclude that chronic restriction of calories strikingly

inhibits the development of tumours, and that amounts of dietary fat, protein and vitamins which are considered to be below the minimum for good nutrition also tend to repress tumour formation. The high standard of experimental design employed by Tannenbaum and Silverstone compels one to accept these generalizations regarding the decreased susceptibility to tumour formation in undernourished animals and this may eventually become applicable to human breast cancer. They remind us, however, that some human cancers occur in the undernourished, for example, primary liver cancer in the African negro and cancer of the hypopharynx in women suffering from iron-deficiency anaemia. On the other hand, the authors quote statistical evidence that the mortality from cancer in men shows a significant fall from a high rate in the obese to a lower rate in the undernourished Their experimental evidence should prompt a carefully controlled inquiry into the relationship between the prevalence of breast cancer and the state of nutrition at the onset of the disease.

CLINICAL CONSIDERATIONS

The First Symptom

Detection by the patient

Relevant to this problem is the tragic delay between detecting the first symptom and first consulting a doctor. Harnett (1952) provided the information on 2,129 cases of breast cancer in women shown in Table XIII

TABLE XIII

Interval from first symptom to first consulting a doctor (months)	*No. of cases*	*Per cent*
1 and under	508	
1— 2	266	44 1
2— 3	164	
3— 4	117	15 3
4— 6	208	
6— 9	136	
9—12	190	
12—18	83	33 3
18—24	119	
24—48	85	
Over 48	97	
Not stated	156	7·3

These figures show that there was serious delay on the part of 48 6 per cent of the patients in seeking medical advice, and in 8 6 per cent the interval was 2–4 years or more

In more than 75 per cent of patients the first symptom noticed is a mass in the breast which, unfortunately, in many instances is painless Table XIV shows the relative frequency of each symptom at the onset (Harnett, 1952)

When the first symptoms were due to local and distant dissemination of the

primary growth (34 patients), metastases were distributed as follows:

	Patients
Vertebral column	14
Liver	5
Lung Brain Supraclavicular nodes	3 in each site
Axillary nodes Skull Femur	2 in each site

TABLE XIV

THE FIRST SYMPTOM COMPLAINED OF IN A SERIES OF 2,129 WOMEN SUFFERING FROM BREAST CANCER

Symptom	*Frequency of occurrence*	
	Per cent	*No. of cases*
Lump in breast	77·4	1,649
Pain in breast	10 0	213
Eczema of skin of breast	2·7	57
Retraction of nipple Referred pain Symptoms due to metastases Bloody discharge from nipple Discharge from nipple	Between 2 and 1	
Lump in axilla Loss of weight and general weakness Not stated	Less than 1	

In 1 6 per cent of patients there were no symptoms, the tumour being discovered by accident during routine examination

THE SIZE OF THE PRIMARY GROWTH

Adair (1949), estimating the size of the primary growth by measuring its greatest diameter when sectioned, found that the smaller the tumour the greater the percentage of 5-year survivals but tumour size had no practical significance in the presence of axillary metastases.

Bloom (1950) decided that whether the tumours are small or large the outlook is uniformly good in Grade I cases and bad in Grade III cases In other words, metastasizing power is independent of size. Kreyberg and Christiansen (1953), who investigated 974 cases of breast canc[illegible] 57 cases in which the pr[illegible] tumour was no larger than a (Swedish) [illegible] that is, 10–12 by 15–[illegible] metres; they concluded that small malig[illegible] tumours as a [illegible] give a decidedly more favourable [illegible] average group of S[illegible] Stage II breast cancers undergoing the [illegible]atment.

Robbins and Bross (1958) confirmed A[illegible]on but [illegible] axillary [illegible] was minimal in [illegible]imal size. [illegible] have excep[illegible] it is well [illegible] primary [illegible] cancer ma[illegible]le to recognize [illegible] be [illegible] large and [illegible] axillary mass (H[illegible]on, 1948).

As on so[illegible], we are forced [illegible]

the behaviour of any breast cancer is determined by the inscrutable biological attributes of the tumour itself.

The Lymphatic Drainage of the Breast

In the early stage of spheroidal-cell carcinoma of the breast involvement of the lymphatics is by malignant lymphatic embolism, and slowing of the lymph flow from obstruction of the lumina of lymph vessels and capillaries is the inevitable consequence. Extensive fibrosis of the stroma, so commonly found in scirrhous cancer, compresses the lymphatics in the immediate vicinity of the growth and seriously limits their capacity to dilate The result is obstruction with stasis which permits the original lymphatic emboli to grow *in situ* Long threads or thicker cylinders of growth are thereby produced and the familiar histological picture of lymphatic permeation, so ably described by Sampson Handley, comes into being.

From the neighbourhood of the tumour there are three main drainage systems: (1) periductal, (2) in the suspensory ligaments of Cooper, and (3) perivascular.

The rich periductal plexuses run in the outer walls of the small, medium and large-sized ducts This system is in direct continuity with the plexuses in the suspensory ligaments and in the interlobular and interlobar connective tissue Both systems drain into the lymph nodes of the axilla or into those which accompany the internal mammary artery. When the barrier to spread imposed by the axillary nodes is breached, growth will automatically spread to the supraclavicular nodes. Both or either of these groups of nodes may be involved depending on the size of the tumour and its location in the breast.

The periductal system, together with the system in relation to the suspensory ligaments and the connective tissue, is in free communication with rich plexuses in the dermis. The involvement of this latter system is responsible for the production of lymphatic oedema of the skin overlying the breast. The area involved varies considerably in size and appearance. It is swollen and slightly indurated. The excretory ducts of the subcutaneous glands and those in connexion with the hair follicles become abnormally prominent as far less oedema fluid collects in the skin which immediately surrounds them than in the skin between them. The openings of these ducts therefore remain widely open and are seen as multiple punctate depressions, 3–5 millimetres apart, lying in the swollen area and producing the familiar *peau d'orange* appearance.

In some cases the subcutaneous oedema is greater, the skin shows erythema and the punctate depressions are less obvious. In others, the whole area is incompletely surrounded by a raised edge—recalling the appearances seen in erysipelas—and when the dermal and subdermal lymphatic plexuses become extensively and progressively obstructed, a gross exaggeration of this picture is produced. This variety of breast cancer is misnamed "inflammatory" cancer; its general features are described later in this section.

When the free growth of tumour cells in the lymphatics of the dermis is unchecked, nodules of secondary subcutaneous growth appear ("satellite nodules") They may be small, closely set, and cover a wide area ("cancer *en cuirasse*").

The spread of breast cancer by perivascular lymphatics has two main routes. The first follows the course of the mammary arteries and their branches This

primary growth (34 patients), metastases were distributed as follows:

	Patients
Vertebral column	14
Liver	5
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Axillary nodes, Skull, Femur	2 in each site

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Robbins and Bross (1958) confirmed Adair's conclusion but considered that the axillary involvement was minimal in tumours of minimal size. This rule must have exceptions because it is well established that a small primary occult breast cancer may be impossible to recognize clinically and yet be accompanied by a large and recognizable axillary mass (Halsted, 1907; Jackson, 1948).

As on so many occasions, we are forced back to the inescapable conclusion that

two the disease regressed. One of these cases was in regression and without progress of the disease 29 months from the operation. Ten primary cases were treated by radical mastectomy and irradiation. The average survival in this group was 7·1 months. Five secondary cases were treated by oophorectomy which in three was followed by regression of tumour growth.



FIG 52.—"Inflammatory" breast cancer Carcinomatous emboli obstructing subepidermal lymphatics (×225) (Reproduced by courtesy of the Editor of the *American Journal of Cancer*.)

INVOLVEMENT OF LYMPH NODES

The close proximity of the supraclavicular lymph nodes to the thoracic duct and the right lymphatic duct makes involvement of these nodes an ominous sign and

system is in continuity with the lymphatics of the deep fascia over the pectoralis major muscle which drain into the axillary lymph nodes. The plexuses in relation to the pectoral muscles are less numerous and complex than the subdermal lymphatics. The second *perivascular route takes the form of* a series of plexuses which follow the course of the perforating branches of the internal mammary arteries to reach the internal mammary chain of lymph nodes.

An additional lymphatic pathway—the perineural lymphatic plexuses which accompany the intercostal nerves—opens up a route which may involve the skin of the back and the dorsal vertebrae and possibly the spinal cord.

"Inflammatory" breast cancer

"Inflammatory" breast cancer is considered here because its clinical manifestations are due to widespread, rapid and progressive occlusion of the dermal and subdermal lymphatic plexuses of the skin of the chest wall (Fig 52). A large area *of the skin over the breast becomes reddened, varying from* a generalized blush to flaming scarlet; it is diffusely swollen, becomes indurated from lymphatic oedema, and shows a typical *peau d'orange* appearance. The swelling may extend beyond the breast to include a large part of the chest wall. There may be a cellular inflammatory response but this is inconstant and may be insignificant. There is little or no fibrotic response around the obstructed lymphatics. Small scattered areas of ulceration may appear in the affected epidermis. It is exceptional for this *to be extensive. With rare exceptions it occurs in large, fatty, pendulous* breasts Without exception the axillary lymph nodes are involved quickly and extensively. Fever and leucocytosis if present are remarkably slight in proportion to the area of skin involved

The disease may occur in a breast in which carcinoma was previously unsuspected —the primary form It may appear suddenly in a breast which for a *long time* has been the seat of a scirrhous cancer—the secondary form. It may follow mastectomy. *The course is substantially the same in both types.* The average total duration of the disease in the primary form is about 20 months but varies from 6 months to 4 years, and the average age at onset is 53 years but varies from 33 to 84 years (Taylor and Meltzer, 1938) It does not complicate any particular variety of breast cancer, has no significant association with pregnancy, and is quite independent of irradiation (Taylor and Meltzer, 1938) In a series of 1,774 *cases of* breast cancer, 2·6 per cent were complicated by the development of this rapid and widespread *involvement of the subdermal lymphatics* (Pratt, 1957)

In the presence of "inflammatory" cancer, mastectomy or any other operative procedure on the breast is followed by an increase in the rate of spread (Lee and Tannenbaum, 1924; Geschickter, 1938; Haagensen and Stout, *1943a and* 1951; Rogers and Fitts, 1956). In the series of Rogers and Fitts, the age range was *26–80 years; 50 per cent of the patients were postmenopausal*, and in 95 per cent there was rapid lymphatic spread to the axillary nodes. The incidence of the disease in the Memorial Hospital, New York, was 1·3 per cent in women and 2 per cent in men (Treves, 1953).

Dao and McCarthy (1957) have treated the disease by bilateral salpingo-oophorectomy alone. Of 13 primary cases, 3 were *treated by this* method and in

Urban (1956) found involvement of the lymph nodes of the internal mammary chain in 35·6 per cent of 290 cases. The details are shown in Table XVI.

TABLE XVI

FREQUENCY OF INVOLVEMENT OF AXILLARY AND INTERNAL MAMMARY NODES IN 290 CASES OF BREAST CANCER

	No. of cases	*Per cent*
All lymph nodes free of growth	130	44 8
Axillary nodes only involved	57	19 6
Internal mammary nodes only involved . . .	22	7 6
Axillary and internal mammary nodes involved .	81	28 0

In the great majority of cases in which the internal mammary nodes were involved, the primary lesion was in the inner half or central part of the breast. In 91 per cent of cases, lymph nodes invaded by growth were present in the first costal interspace; 89 per cent in the second, decreasing to 13 per cent in the fifth.

PATHOGENESIS

Does chronic cystic mastitis predispose to breast cancer?

The cysts in chronic cystic mastitis may be large, small or microscopic. Whatever their size they are almost always associated with easily recognizable hyperplasia of the epithelium of the duct system This combination constitutes the commonest breast lesion in premenopausal women, and "cystic hyperplasia" (Willis) as a synonym for chronic cystic mastitis is to be commended Its high incidence over a wide age range in the breasts of normal women who give no history of previous breast disease is shown in Table XVII.

TABLE XVII

INCIDENCE OF CYSTIC HYPERPLASIA IN NORMAL WOMEN WHO HAVE NO HISTORY OF PREVIOUS BREAST DISEASE

Series reported by	*Total breasts examined*	*Incidence of chronic cystic mastitis per cent*
Frantz and his colleagues (1951) . .	225	53*
Foote and Stewart (1945) . .	200	65

* In 19 per cent the cystic change was gross

Gross naked-eye cystic disease may be widespread throughout both breasts and cancer is not commonly found when this is the dominant change because cancer arising in the walls of a cyst is rare The relationship of epithelial hyperplasia to breast cancer thus becomes the basic problem.

EPITHELIAL HYPERPLASIA

Epithelial hyperplasia may take two forms: (a) papillomatosis of the duct system

very greatly increases the probability of invasion of the venous blood stream and the lungs. Involvement of the internal mammary chain carries the danger of extension into the anterior mediastinum, of invasion of the subpleural lymphatics and of the perineuronal plexuses of the intercostal nerves.

Supraclavicular nodes

Haagensen and Stout (1943*b*), in investigating 98 cases in which the axillary lymph nodes were involved, made the fundamental observation that when the highest node of the axillary group was involved there was a high probability that the supraclavicular group was also invaded. It is also agreed that when lymph node recurrence follows complete surgical excision of the axillary nodes the recurrence will be found in the supraclavicular group.

Andreassen and Dahl-Iversen (1949) found these nodes to be involved in 33 per cent of cases in which the axillary nodes were invaded. In all cases in which the supraclavicular nodes contained growth the axillary nodes were already invaded. Unsuspected invasion of the supraclavicular nodes was found in 17 per cent of their series.

The internal mammary nodes

Handley and Thackray (1947) found histological proof that the internal mammary lymph nodes may often be invaded at the same time, and sometimes before carcinoma has reached the axilla. In five unselected cases of breast cancer, a lymph node was removed from the second intercostal space of the affected side at, or after, radical mastectomy. Four cases had secondary growth in this internal mammary lymph node, axillary deposits were present in two In the remaining case the internal mammary node was free from growth and there were no axillary metastases. They suggested the introduction of a modified technique of radical *mastectomy to include removal of the second space internal mammary* lymph node, since histological examination of this node might increase the accuracy of prognosis and influence the planning of post-operative treatment by irradiation On further elaboration of their first observations, Handley and Thackray (1954) published the details given in Table XV of the overall frequency *of involvement* of the axillary and internal mammary nodes in a series of unselected hospital patients.

TABLE XV

FREQUENCY OF INVOLVEMENT OF AXILLARY AND INTERNAL MAMMARY NODES IN 150 UNSELECTED BREAST CANCER PATIENTS

	Situation of primary growth in breast		*Totals*	
	Inner half	*Outer half*	*No. of cases*	*Per cent*
[illegible] nodes free of growth	16	33	49	32·7
[illegible]	12	40	52	34 7
[illegible]	6	2	8	5·3
[illegible]	27	14	41	27·3
Total . .	61	89	150	100 0

lesions prove to be nothing more than benign duct papillomatosis There is no doubt that the malignant potentialities of papillomatosis of the breast ducts has been greatly overstressed, nor can it be denied that "the actual number of cases of innocent papillomatosis which become malignant must necessarily be a very minute one" (Foote and Stewart, 1945). On the other hand, it is difficult to deny that innocent papillomatosis is the precursor of 15 per cent of breast cancers.

Intralobular epithelial proliferation

Approximately 15 per cent of breast cancers appear to originate in the epithelium of the duct system above the lobular alveolar level. It is difficult to define the origin of the spheroidal-celled undifferentiated growths which constitute 75 per cent or more of all breast cancers. Relevant histological evidence suggests that they may originate within the mammary lobule from the epithelium of lobular ducts, the fine ductules which arise from them, or the gland acini in which these ductules terminate Dawson (1958), whose conclusions are based on the study of large sections of the breast, believes that epithelial proliferation within the mammary lobule is of two kinds lobular adenosis and epitheliosis.

"Lobular adenosis"

"Lobular adenosis" is an irregular and focal counterpart of the rapid physiological growth of the breast as seen in the whole organ at puberty and during pregnancy and needs for its accomplishment a synergistic combination of pituitary growth hormone and prolactin together with oestrogenic and progestational steroids "Physiological lobular adenosis" can be readily produced in small mammals by these hormones and shows rapid regression when they are withheld

Adenosis is characterized by an overall increase in the number and size of functionally competent lobules of physiological pattern, and even when excessive and irregular as in cystic hyperplasia it is not considered by Dawson to be a source of malignant disease One good reason for this belief is that adenosis shows a strong tendency to complete regression by a process which recalls the involution of the mammary gland which normally follows interruption of lactation, abortion, ovariectomy or the "natural castration" of the menopause. It also recalls the regression of experimental adenosis when hormones are withdrawn

"Epitheliosis"

In this variety of intralobular proliferation there is free multiplication of the epithelium lining the terminal ductules of the lobule This cellular hyperplasia, by enlarging the ductules and gland acini, completely and uniformly obliterates their lumina Similar degrees of irregular epithelial hyperplasia are induced by the administration of hormones to small mammals and the process can be arrested by hormone withdrawal. Epitheliosis arising as a patchy lesion in a hyperplastic breast is a reversible lesion.

During periods of active hyperplasia, cell proliferation is strictly intraductal and there is no sign of infiltration. In a small but *completely unknown* proportion of cases, "intraductal lobular epitheliosis" becomes extraductal and microscopic

above the level of the terminal lobules, (b) epithelial hyperplasia within the mammary lobules.

Papillomatosis

Types

(1) Papillomas in the walls of the main ducts, close to the nipple—few in number, large and often single.

(2) Multiple papillomatosis of the duct system deeper in the breast and below the main ducts, but above the level of the lobular-alveolar zones. This is of three types:

(a) Affecting medium-sized ducts: the papillomas are discrete, visible by the naked eye or hand lens, and very frequently involve a medium-sized duct and many of its branches.

(b) Closely-set, innumerable and microscopic papillomas involving the whole or a large part of the duct system of one or more lobes.

(c) A combination of (a) and (b) above.

Frequency and degree

The percentage frequency and degree of papillomatosis in cancerous and cancerous breasts is shown in Table XVIII and of degree in Table XIX.

TABLE XVIII

PERCENTAGE FREQUENCY AND DEGREE OF PAPILLOMATOSIS IN CANCEROUS AND NON-CANCEROUS BREASTS—DATA OF FOOTE AND STEWART (1945)

Decade	*Non-cancerous per cent*	*Cancerous per cent*
30—40	18	24
40—50	40	40
50—60	23	28
Macroscopic papillomas	Predominate	Uncommon
Epithelial proliferation	Orderly	More proliferative and irregular

TABLE XIX

	Slight per cent	*Moderate per cent*	*Marked per cent*
Non-cancerous	53	27	20
Cancerous	64	25	11

The figures given in Table XIX lead to no very definite conclusion.

For long periods the papillary structure of this hyperplastic process may remain intact, become obliterated by fibrosis, or show increased cellular proliferation, an impressive increase in cellularity and some of the changes associated with anaplasia, especially loss of cell polarity and the nuclear changes associated with rapid growth. A histological picture is then seen which suggests a transition between innocent papillomatosis and "infiltrative duct cancer". This has been described as "non-infiltrating cancer". Foote and Stewart (1945), although believing in the reality of this transition, hold the strong belief that the vast majority of such

feature. For these reasons papillary carcinoma when compared with spheroidal cell carcinoma has a considerably longer delay before bloodstream dissemination and, therefore, a longer survival period.

Medullary carcinoma with lymphocytic infiltration

The origin of this deceptive growth, which constitutes 4 per cent of all breast cancers, has been clearly traced to the duct system and although composed of broad anastomosing cellular columns and masses, long and patient search usually reveals the branching vascular stalks of a papillary cancer (Moore and Foote, 1949). Between the masses of tumour cells there is invariably a copious infiltration of the stroma by abundant lymphocytes unrelated to necrosis and possibly a "host-reaction". Fibrosis of the stroma does not occur (Stewart, 1950) The tumour is remarkably bulky, globular, soft and circumscribed and the cut surface bulges on section. Haemorrhage and necrosis are common. It usually reaches a large size and may even fungate before axillary metastases appear. When this has occurred there is again a long interval before dissemination by the blood stream takes place. In the 52 cases reported from the Memorial Hospital, New York, 83 per cent of the patients were still alive at the end of 5 years although half of these had bulky axillary nodes (Foote and Stewart, 1945).

Mucoid (colloid) carcinoma

This description is limited to tumours which are grossly and uniformly mucoid on naked-eye examination. Small foci of mucoid degeneration are commonly found in breast cancers and have no prognostic significance. Dawson (1958) considered that colloid breast cancers arise by malignant transformation of intracystic papillomas and at an early stage when the tumour is still well defined, have the relatively favourable outlook of circumscribed papillary cancer They have, however, a stronger tendency to infiltrate, and in their later stages the prognosis approximates to that of spheroidal-cell carcinoma with a fibrous stroma.

Spheroidal-cell carcinoma with a fibrous stroma (scirrhus mammae)

The site of origin in the mammary tree of this, the most common variety of breast cancer, remains a matter for conjecture. Its outstanding characteristic is rapid cellular proliferation with its usual accompaniments of anaplasia, lack of differentiation and a predominating spheroidal-cell structure.

There are two alternatives:

(1) That any variety of breast cancer, whether it arises in the duct system or within the lobules may, by virtue of rapid multiplication of its cells, become a spheroidal-cell carcinoma and develop a fibrous stroma.

(2) That spheroidal-celled carcinoma with a fibrous stroma is not a common end-product of several types of breast cancer but originates within the lobule and from cells which have a higher "growth potential" than the epithelium of the duct system *This conception*, which must remain hypothetical, receives some support from the fact that spheroidal-cell carcinoma generally arises in the peripheral or lobular zone of the breast and also that small peripheral cancers with a diameter of 1 centimetre or less have a pure spheroidal-cell structure and lack the structural complexity of the duct

infiltration outside the confines of the lobule of origin can be seen. For the sake of convenience we may call this lesion "malignant epitheliosis". In doing so we would again be confronted, as in papillary hyperplasia, with a histological picture incapable of clinical recognition which may represent a transition between hyperplasia and neoplasia. If further investigation establishes this to be a true transition, then "malignant epitheliosis" would become "mammary carcinoma *in situ*". Kiaer (1954), in a 96 per cent follow-up of 334 cases showing the combination of cystic hyperplasia with adenosis or epitheliosis as the dominant feature, found that 45 per cent developed cancer. In those showing mainly adenosis, only 3 per cent became malignant.

It is of great interest to compare Dawson's investigations with those of Foot and Stewart (1945). They describe a series of intralobular hyperplasias which are very similar and possibly identical with Dawson's "adenosis" and "epitheliosis" and by studying a series of histological transitions they have described a lobular lesion which they believe to be carcinoma *in situ*.

The work of these observers on either side of the Atlantic has opened up an important field of inquiry into the pathology of the mammary lobule which may lead to a better understanding of the pathogenesis of spheroidal-cell carcinoma. The problem is a remarkably difficult one.

The Common Varieties of Breast Cancer

Papillary carcinoma

This category includes the following conditions: intraductal papillary carcinoma; infiltrating papillary carcinoma, and medullary carcinoma with lymphocytic infiltration.

Intraductal papillary carcinoma

Intraductal papillary carcinoma must be regarded as a histological "transition": it has no definitive clinical picture. Long histological experience is required for its diagnosis. It has been frequently misdiagnosed and the incidence of cancer arising from duct papillomatosis has been falsely over-estimated. Nevertheless, its confident recognition by the pathologist calls for action on the part of the surgeon.

Infiltrating papillary carcinoma ("duct cancer")

The hall-mark of infiltrating papillary carcinoma, which accounts for at least 10 per cent of all breast cancers, is its papillary structure which, although often obscured, still remains recognizable as a system of anastomosing finger-like vascular stalks thickly clothed by tumour cells showing little or no polarity and varying degrees of anaplasia. These tumours produce little or no fibrosis in the scanty stroma in which they lie; they are therefore bulky, mobile, soft, rounded, well defined and tend to be roughly pyramidal with the apex towards the nipple. Not infrequently the tumour shows necrotic and haemorrhagic areas. Microscopic infiltration is usually obvious but there is considerable delay before the periductal and perivascular lymphatics are freely infiltrated. These characters are in sharp contrast with the hard, discoid, scirrhous cancer whose stroma is densely fibrotic and in which free lymphatic permeation is a characteristic and remarkably early

TABLE XX

Author	Total No. of cases	Occurrence of bilateral breast cancer (percentages of all cases)	
		Metastatic	*A second primary*
Harrington (Mayo Clinic, 1946)	6,559	4·5	1 0
Harnett (London, England, 1952)	2,129	2 53	0·3
Farrow (New York, 1956)	5,576	3·2	0 4

Farrow applied the following stringent criteria in classifying his cases:

(1) *For a second primary.*—The tumours must be of approximately the same size. There must have been no treatment to either breast. There must be no evidence of lymphatic spread across the middle line, of subcutaneous nodules, or of distant metastases

(2) *For involvement of the second breast by spread of disease from the first.*—The primary in the first breast must have been adequately treated. There must be no local recurrence or distant metastases during the interval between the treatment of the first tumour and the diagnosis of the second.

It appears from the records quoted that of 1,000 unselected cases of breast cancer there are likely to be approximately 5 cases of bilateral primary breast cancer. The incidence of multiple independent neoplasms in all types of neoplasia is said to be between 20 and 40 per 1,000 (Warren and Gates, 1932) and this incidence is more than would be expected to arise by chance alone.

Moore (1951) asserted that "a patient with one cancer is six times more apt to develop a second cancer than would be expected from chance alone".

Statements such as these must be accepted with caution because they carry the implication that the first cancer is responsible for increased susceptibility and the development of the second primary.

Apart from the statistical evidence which involves complex computation, surgeons and pathologists generally believe that the overall incidence of "double breast cancer" is higher than could occur by chance. This belief is expressed by Foote and Stewart (1945) in the following words: "The one most common precancerous lesion of the left breast is a cancer in the right breast and *vice versa*".

Breast Cancer in Pregnancy and Lactation

The mean age of onset of breast cancer first detected during pregnancy is 35 years; it is uncommon above the age of 42 years or below the age of 28 years. Approximately 80 per cent of breast cancers arise after this period, 75 per cent occurring in postmenopausal women. As there are no reasons for supposing that pregnancy increases susceptibility to breast cancer during the narrow age range when it occurs, age at onset in all probability accounts for the great rarity of this variety of the disease.

Breast cancer arising during pregnancy has a sinister reputation which is largely accounted for by the fact that the tumour mass in the breast is regarded by the patient as an integral part of the rapidly growing gland It is notorious that the presence of the tumour is not usually reported until axillary metastases

cancers It is also supported by Dawson's demonstration within the lobule of the *histological sequence:*

epitheliosis——→malignant epitheliosis——→infiltrating carcinoma
and by the sequence described by Foote and Stewart=
lobular hyperplasia——→lobular carcinoma *in situ*——→infiltrating lobular carcinoma

It is at the moment impossible to select either of these alternatives as the more probable but it would appear that further investigation of the growth potentiality of the epithelium within the mammary lobule is likely to be rewarding.

Less Common Varieties of Breast Cancer

Paget's disease

Paget's disease is generally accepted as a primary carcinoma of the nipple ducts extending into and replacing the epidermis of the nipple and surrounding skin Its mean incidence from the large series published by Wakeley (1951), Saner (1950) and Lane-Claypon (1928) is 0·16 per cent of all types of breast cancer. It will be recalled that Paget believed the disease of the nipple to precede the development of cancer in the breast and Willis (1953) proposed that Paget's disease should be regarded as a carcinoma *in situ* of the nipple skin with a coexistent but unrelated tumour of the nipple ducts Cases are recorded in which the lesion was not accompanied by breast cancer and others in which the breast cancer was so deep-seated that spread by continuity to the skin of the nipple was highly improbable. Dawson (1958) has taken the problem further. She has investigated the histological changes in the epidermis in 200 cases of simple indrawn nipple and found lesions indistinguishable from those which occur in association with classical Paget's disease. The lesion is not easily recognizable clinically as the change was strictly confined to the skin of the indrawn nipple. It was often associated with breast cancer but occurred in its absence. Dawson points out that Paget's epidermal lesion may occur in extramammary sites, especially the "genital skin" containing apocrine glands, that is, the vulva, glans penis and the skin of the thighs She also notes that Bowen's disease, in which carcinoma *in situ* occurs in its typical form, closely resembles the skin lesion of Paget's disease.

Squamous metaplasia in breast cancer

Tumours showing widespread squamous transformation are rareties and have a highly malignant reputation. Microscopic foci of squamous metaplasia, however, are not uncommonly found in papillary cancer and their presence does not alter the prognosis of the main tumour process.

Bilateral Breast Cancer

The mammary glands are unique among the paired organs in sharing the rich subcutaneous lymphatic field which lies between them. A second cancer may therefore arise as a secondary growth from a cancerous breast on the other side, or a cancer in one breast may be accompanied or followed by a second and independent primary growth in the other. Table XX summarizes three large series of reported cases.

Cancer cells in the blood

It has been shown beyond all reasonable doubt that cancer cells can be recognized in blood films. Sandberg and Moore (1957) found that of 36 breast cancer patients in whom the disease was advanced but not terminal, 18 had cancer cells in the peripheral blood, and of 105 cases of adenocarcinoma, cancer cells were found in 45 and absent in 60. In 12 patients whose blood contained no cancer cells the breast was manipulated, after which cancer cells appeared in the blood in one case. Roberts and his colleagues (1958) examined 100 cancer patients. In 72 the disease was described as "curable" and cancer cells were found in blood films in 16·7 per cent. In 28 regarded as "incurable", 31 per cent had positive blood films. Of 25 breast cancer patients, 23 were regarded as "curable" and of these, 4 had positive blood films, whilst both of 2 "incurable" patients showed blood invasion. This new approach promises to throw light on the otherwise unpredictable time in the course of breast cancer when the blood stream becomes invaded; the results obtained suggest that blood invasion takes place independently of lymphatic involvement.

Site of distant metastases

The exceptionally wide distribution of blood-borne metastases in breast cancer is notorious. The general distribution as found post mortem according to Willis (1952) is:

	Per cent
Lung and pleura	66
Skeleton	50
Liver and peritoneum	50
Central nervous system	20

Skeletal metastases are found in the spine, pelvis, femur, ribs and skull in this order of frequency.

Metastases in the endocrine organs

Many observers have stressed the frequency of metastatic deposits in the adrenal cortex. In one post-mortem series (Willis, 1952), the incidence was 20 per cent. In another, reported by Warren and Witham (1933), it was 32 per cent. Of particular interest is the incidence in surgically excised adrenals. Pizzetti and Sirtori (1958) found involvement, almost entirely limited to the cortex, in 30·8 per cent of 68 cases; 14·7 per cent being bilateral. Pyrah (1956) found an involvement of 35 per cent in 75 patients; Cade (1955) found a 60 per cent involvement in [illegible]

[illegible]

gland, or as widely disseminated microscopic growth throughout the cortex.

Ovarian involvement was found in 6 6 per cent of Willis's post-mortem series Pizzetti and Sirtori (1958) found an 18 per cent involvement of ovaries excised for metastatic breast cancer in a series of 72 patients: in 5·5 per cent metastases were bilateral.

are present. Of 92 patients, 85 per cent had axillary metastases when first examined (Harrington, 1938). Of 78 patients in this group, 92 per cent were dead within 5 years—usually from 1 to 3 years—and blood-borne metastases were frequently found within a year after treatment (Harrington, 1941). All published reports since 1941 confirm these statements.

It will be noticed that 8 per cent of patients in Harrington's group pursued a less rapid course, and it is usually agreed that although the prognosis is grave it is not hopeless as an occasional patient will pursue the usual unpredictable course of breast cancer with axillary metastases and uncomplicated by pregnancy. Of 14 cases in whom axillary metastases were not present, 43 per cent were dead within 5 years. The far higher mortality in the first group points to the fact that, in some way, the presence of axillary metastases is responsible for the sinister reputation of the disease.

It is sometimes stated that when breast cancer is recognized for the first time during lactation the disease pursues an even more rapid course provided axillary or distant metastases are present. Published results do not clearly demonstrate this difference and the course of lactational cancer appears to have the same characteristics as pregnancy cancer.

Patients who have had radical treatment for breast cancer and subsequently become pregnant do not appear to show a significantly higher mortality rate after 5 years than those whose post-operative course is uncomplicated by pregnancy.

Any explanation for the "hurricane" course pursued by breast cancer with involvement of the axillary nodes during pregnancy must be speculative. It can be argued that some of these growths are hormone dependent and that the very large amounts of mammogenic and oestrogenic hormones produced by the placenta during pregnancy may induce rapid growth of the tumour. This supposition is difficult to accept as both the pregnant breast and its tumour will probably take as much hormone as they need and no more. It seems to be more probable that the operative factor is the enormous increase in the total cross-sectional area of two capillary fields, one carrying blood, the other lymph.

Spread of Breast Cancer by the Blood Stream

The mean duration of life in untreated breast cancer is 38 months and death is almost invariably due to the effects of blood-borne distant metastases which become clinically recognizable only after the growth has involved the regional lymph nodes. This suggests that invasion of the venous blood stream is conditioned by and is a direct secondary consequence of lymphatic involvement. It is impossible to accept this generalization. Of every 100 patients submitted to radical mastectomy and in whom histological examination subsequently provides no evidence of involvement of axillary nodes, at least 18 are dead of blood-borne metastases within 5 years. It is true that this 5-year mortality rate rises to at least 55 when the axillary nodes are invaded, but the degree of axillary involvement does not enable us to predict with any degree of certainty that the blood stream has been invaded. Furthermore, any group of breast cancer patients must unavoidably contain cases of papillary carcinoma in whom blood invasion tends to be long delayed.

Relation of the reticulo-endothelial system

Of the small or microscopic foci of metastatic tumour lying in deeply placed organs and probably implanted before removal of the primary growth, at least 50 per cent lie in the haemopoietic bone marrow, for after a long latent period varying from 5 to 30 years they may become reactivated, grow vigorously and produce skeletal metastases. Kettle (1913) drew attention to the presence of metastatic foci of dormant cancer cells in the pulp of the unenlarged spleen and suggested that as such growths lie in the territory of the portal vein they may reach the liver, become reactivated in this new environment and produce a clinically obvious tumour. These observations suggest that cancer cells in the blood stream and filtered out by reticulo-endothelial organs have a tendency to become dormant. It will be recalled that metastatic deposits are not infrequently found in the cortex of surgically excised adrenal glands Such deposits are often microscopic, the adrenals may be neither enlarged nor deformed, and it is uncommon to find such metastatic growth extending into surrounding tissues.

The frozen cancer cell

It has been demonstrated by Craigie (1954) that tumour cells can be kept alive in a frozen and anoxic state for periods which are comparable in time to those during which tumour cells remain temporarily dormant in human tissues. Such cells emerge from the frozen state with no apparent deterioration in their biological or malignant characteristics In one of Craigie's experiments malignant cells were maintained at $-70°$C. for 5 years When thawed out and grafted into animals of the species from which they were obtained they grew even more rapidly than before freezing These experiments demonstrate that malignant cells, in common with certain normal cells, have remarkable powers of adaptation to a grossly unfavourable environment, and after long periods of mitotic arrest are still capable of proliferation and infiltration in the favourable environment provided by normal living tissues.

The hormonal environment

Experiments by Gardner (1945) are relevant to the problem of hormonal environment He studied certain interstitial cell tumours of the mouse testis whose growth after grafting is strictly conditioned by the administration of oestrogen; when oestrogen is withdrawn the tumour regresses and it is remarkably difficult to identify tumour cells at the site of the tumour even by serial section. In a group of control animals the tumour was grafted and oestrogen withheld. No tumours appeared during a long period of observation. Oestrogen was then administered and the majority of animals developed large testicular growths. These experiments permit the speculation that metastatic deposits may become dormant in an environment lacking a hormone essential for cellular proliferation.

Foulds (1949) has described a tumour of the mammary gland in certain strains of mice which grows and infiltrates during pregnancy, promptly regresses after parturition and remains latent until reactivated at the next pregnancy, presumably by a hormonal environment probably provided by the placenta.

Metastatic deposits in surgically excised pituitary glands are usually difficult to identify as the organ is removed piecemeal. A series of 25 patients admitted to St. Bartholomew's Hospital with metastatic breast cancer was evaluated for hypophysectomy by estimating oestrogen excretion (Bulbrook and his colleagues, 1958c). Two cases went into spontaneous objective regression and in view of the possibility that this was due to pituitary destruction from metastatic involvement hypophysectomy was not performed. The remaining 23 cases were hypophysectomized. Of these, 4 were found to have microscopic metastases in the pituitary gland itself, in 2 the pituitary was invaded from growth originating in the sphenoid bone or in basal meninges around the pituitary fossa or in both. Both cases in which pre-operative regression occurred were found at post-mortem examination to have pituitary metastases—one in the pituitary, the other spreading into it from the surrounding tissues (unpublished data).

Spontaneous hormone deprivation

Metastatic destruction of the pituitary inducing a growth regression is likely to prove to be more common than the lack of published records suggests. Total metastatic destruction of the pre-menopausal ovary may induce a spontaneous growth regression in pre-menopausal breast cancer by deprivation of ovarian steroids. Treves (1954) has reported this sequence in a woman of 32 years who, following radical mastectomy for breast cancer, developed widespread metastases. Her disease regressed spontaneously, remained quiescent for 3 years, and then recurred. The ovaries were found at post-mortem examination to be extensively involved by metastatic growth.

A similar instance, in which metastatic destruction of the adrenal cortex had occurred, is reported by Cade (1954). A spontaneous regression of multiple bilateral pulmonary metastases from breast cancer coincided with the development of an Addisonian state. Thorn's test showed complete absence of adrenal cortical function and the administration of cortisone was followed by a satisfactory therapeutic response.

Dormant Cancer *

The period elapsing between the radical excision of a breast cancer and the appearance of local or distant recurrence varies between the remarkably wide limits of a few months to 30 years. It is probable that the tumour cells responsible for local recurrences are deposited as a cellular contamination of the wound during operation (Leading Article, 1958). Invasion of the blood stream may be due to the same cause but is rather more likely to be an independent event preceding the operation. In any case, when the period between operation and recurrence is measured in years it is permissible to assume that during this time the displaced tumour cells are in a state of mitotic arrest but retain, for periods of time measured in years, their innate capacity to grow rapidly and infiltrate widely (Hadfield, 1954).

* *Dormant cancer* may be confused with Occult cancer which refers to a primary breast cancer so small that it is difficult to identify on clinical examination and yet is accompanied by clinically obvious metastases. *Dormant cancer* refers to a cancer recurrence whose cells have ceased to grow.

TABLE XXI

	Contributed by		
	Pituitary gland	*Ovary*	*Adrenal gland*
Growth of duct system	Growth hormone	Oestrogen*	Corticosteroids*
Full glandular differentiation	Growth hormone Prolactin	Oestrogen Progesterone*	Corticosteroids

* Ovarian oestrogen production is controlled by pituitary gonadotrophin, ovarian progesterone production by pituitary prolactin, and adrenal corticoid production by ACTH

Hadfield and Young (1958), using the rudimentary mammae of the male weanling mouse, totally hypophysectomized at the age of 23 days, obtained the results given in Table XXII.

TABLE XXII

Hormones given	*Result*
Oestrone alone Progesterone alone Oestrone + progesterone Growth hormone alone Prolactin alone Growth hormone + prolactin	The mammary atrophy which inevitably follows total hypophysectomy continues unchecked
Growth hormone + oestrone + progesterone	A prolific mammary growth response characterized by striking mitotic activity and rapid epithelial proliferation

These experiments show that the oestrogenic and progestational steroid hormones cannot induce a mammary growth response in the absence of the pituitary gland and that pituitary hormones acting alone are unable to do so.

The part played by growth hormone

Growth hormone, provided that it acts in synergism with an oestrogenic steroid, induces the production of a duct system During this preliminary stage of breast development, which has been called the mitotic phase, the intensity of epithelial proliferation reaches its maximum (Hadfield and Young, 1958). For this reason it appears that the synergistic combination of pituitary growth hormone with an oestrogenic steroid may prove to be a major factor in the maintenance of a rapidly proliferating hormone-dependent spheroidal-cell carcinoma of the human mammary gland in which glandular differentiation is either rudimentary or absent

The adrenal "take-over"

There is a substantial body of experimental evidence strongly suggesting that the tissue of origin of oestrogenic and progestational steroids in castrated animals is the adrenal cortex, and it is reasonable to suppose that in postmenopausal women oestrogen and progesterone production by the ovary ceases and is taken

The mechanism whereby dormant cancer cells in human tissues become reactivated is a matter for speculation. Gordon-Taylor (1948) believes that the stress of a severe illness or a surgical operation, or of treatment by irradiation is capable of reactivating a dormant focus of metastatic cancer.

Hormone Dependence in Breast Cancer

The cells of approximately one-half of all spheroidal-cell carcinomas of the breast are remarkably sensitive to their hormonal environment and investigation of this characteristic has led to the formulation of the hypothesis of hormone dependence This postulates that cellular proliferation in hormone dependent breast cancers will cease if the host is unable to supply the tumour with adequate quantities of the hormones essential for the growth and development of the normal mammary gland

The major implications in this hypothesis are well supported by the results of surgical excision of the ovary, adrenal gland or hypophysis in women with breast cancer It should, however, be stressed that hormone dependence is not always a permanent characteristic; it may eventually be proved that dependence is sometimes only partial, that the hormones produced by the breast cancer patient are not strictly identical with those of normal women, or that their rate of production is irregular and physiologically abnormal

Hormones required for normal mammary growth

The basic information required for the solution of this problem and for the rational treatment of breast cancer by hormone therapy or endocrine ablation must come from the experimental endocrinologist, for if we are to deprive a breast cancer of all the hormones required for normal mammogenesis we must know the nature and origin of each of them.

The growth and development of the normal mammary glands proceeds in three stages:

(1) A mitotic phase characterized by epithelial proliferation and culminating in the production of a duct system.
(2) The phase of glandular differentiation leading to the formation of a functionally competent gland.
(3) The establishment of secretion.

The available evidence, clinical, physiological and experimental, leads to the inescapable conclusion that each of these phases is controlled by a specific synergistic combination of one or more protein hormones produced by the anterior pituitary gland, together with one or more steroid hormones produced in the follicles and corpora lutea of the ovary or in the cortex of the adrenal gland.

The specific hormonal environment required by the rat for each of these phases of normal mammary growth has been studied experimentally over the last 25 years by Lyons and his colleagues (1955) at the University of California, and a full and authoritative review of this complex problem has recently been published (Lyons, 1958).

Lyons has shown that the hormones concerned in bringing the mammary gland of the rat to the status of full functional competence are as given in Table XXI.

TABLE XXI

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over by the adrenal cortex. Adrenal ablation in women with postmenopausal breast cancer induces a temporary growth regression in approximately 50 per cent of cases and provides further evidence in favour of this contention.

In the large majority of patients in whom breast cancer regresses after adrenalectomy, the disease recurs in approximately 6 months. It appears, therefore, that it is impossible permanently to remove the whole of the oestrogen-producing tissue in the body.

It is quite clear that the regression of tumour growth temporarily induced by castration and adrenalectomy is due to deprivation of oestrogenic and perhaps of progestational steroids. This deprives the tumour cells of oestrogen and robs the pituitary of the physiological stimulus which normally releases prolactin. When oestrogen production is again established, therefore, prolactin release induced by oestrogenic stimulation will be re-established at the same time. Theoretically, this situation can be rectified only by hypophysectomy.

Endocrine Ablation in Human Breast Cancer

Oestrogen excretion

In unselected cases ablation of the ovaries, adrenals or hypophysis will usually induce a fall in oestrogen excretion. A growth regression can be expected only in hormone-dependent tumours, which constitute about 50 per cent of all breast cancers. The following accounts of oestrogen excretion (Bulbrook and his colleagues, 1958*a*, *b*, *c*) were based on biochemical estimations of the three common oestrogens using Brown's (1955) method.

Following surgical castration

In premenopausal women.—The excretion of oestrogen falls to a low level after operation but does not reach zero levels. This low level of excretion continues. Temporary objective growth regressions lasting for about 6 months are induced in 25 per cent of cases. Relapse is eventually inevitable and a rise in oestrogen excretion to a high level accompanies it.

In postmenopausal women.—The stress of the operation may induce a short temporary rise in excretion. Oestrogen levels then remain at the pre-operative level and the clinical course of the disease is unaltered.

Following adrenalectomy (with or after castration)

A marked fall in oestrogen excretion is induced but excretion at low levels is often maintained though showing considerable fluctuation.

Patients developed objective growth regressions during periods of low oestrogen excretion and a rise in excretion occurred when patients in regression relapsed.

In some patients with progressive disease and a low oestrogen excretion adrenalectomy failed to induce a regression but subsequent hypophysectomy was able to do so. Two patients in whom a low pre-operative oestrogen remained unchanged by adrenalectomy went into regression possibly related to deprivation of an adrenal progestational hormone.

Following surgical hypophysectomy

In these cases hypophysectomy followed oophorectomy with or without adrenalectomy. Hypophysectomy invariably reduces oestrogen levels. One of two patterns of oestrogen excretion then evolves:

(1) The pre-operative levels of oestrogen being low, the operation commonly induces a fall.
(2) The pre-operative level being high, operation either induces a significant fall to a level at which excretion continues indefinitely, or does not materially change the oestrogen level.

Regression of growth was observed to accompany both types—showing that regressions could occur whilst oestrogen was being excreted.

Two patients had progressive disease in the absence of detectable oestrogen. In both instances hypophysectomy induced growth regression. One, a postmenopausal woman, had not been subjected to any previous ablation operation. The other had failed to react to a previous oophorectomy and adrenalectomy.

Results of endocrine ablation

Table XXIII summarizes published results from various sources

These results provide strong evidence that surgical ablation of the relevant endocrine organs is an ethical procedure Endocrine ablation and additive hormone therapy are the only therapeutic weapons available at the present time which can induce a regression of tumour growth in organs and tissues inaccessible to surgery

TABLE XXIII

THE RESULTS OF ENDOCRINE ABLATION. A SUMMARY OF PUBLISHED SERIES

Author	*No of cases*		*Improvement Per cent*
	Total	*Selected*	
Adrenalectomy series			
Huggins (1955)	100		38 0
		95	40 0
Taylor (1956)	60		36 0
Lipsett and his colleagues (1957)	70		51 4
		67	55·7
Cade (1958)	137		58 0
Hellstrom and Franksson (1958)	150		51·0
Pyrah (1958)	75		52 0
Hypophysectomy series			
Luft and his colleagues (1956)	52		42·3
		42	53 6
Ibid (review of literature)	197		56 0
Ray and Pearson (1956)	74		48 6
		67	53 3
Kennedy, French and Peyton (1956)		28	64 0
Baron, Gurling and Radley Smith (1958)	52		42·3
		33	66 6
Matson (quoted by Jessiman) (1958)	25		54 0
Scowen (1958)		15	60 0

and irradiation. In the regrettable absence of any reliable test for pituitary functio[illegible] these operations are experimental and the results provide substantial proof tha[illegible] one-half of all human breast cancers are hormone dependent, the mean percentag[illegible] of regressions induced by both procedures in 1,035 patients being 50·9 per cent.

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part in maintaining an optimum yield of milk. It is likely that several of these same hormones are capable of promoting the growth of breast cancer and there is good evidence that oestrogens and growth hormone do so The effects of progesterone and prolactin may well prove significant, but they have not yet been studied thoroughly.

The term "hormone-dependent" has been introduced to describe those growths whose development or progression are influenced by hormones. Evidence of hormone-dependence comes from four main sources. First, animal experiments indicate that oophorectomy reduces the incidence of spontaneous tumour formation in the breast and that stimulation with oestrogens increases it (Pyrah, 1956) Similarly, oophorectomy for any reason in women seems to afford some protection against the development of breast cancer. Secondly, the administration of oestrogens or of growth hormone to women with bony metastases from breast cancer may

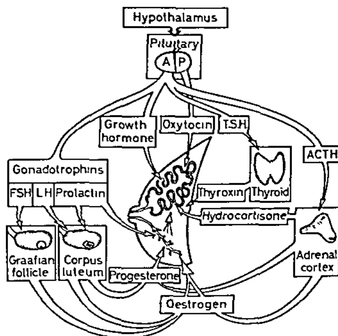


FIG. 53.—The main hormones which control the development and function of the breast.

stimulate the rate of growth of the lesions and increase the excretion of calcium (derived from the eroded bone) in the urine (Jessiman, 1958; Pearson and his colleagues, 1957). Thirdly, the administration of certain hormones and the removal of the ovaries, the adrenals or the pituitary may halt the disease and cause it to regress. Fourthly, the disease may be influenced by natural events which are associated with endocrine changes. Growth may be accelerated during the pre- [illegible] and during pregnancy and [illegible] ncide with [illegible] e growths the menopause (Hadfield and Holt, 1956). It is probable that [illegible] in women are oestrogen-dependent (Pearson and his colleagues, 1955), but the proportion that are dependent on hormones of some type may be much higher (Jessiman, 1958). Hormone-dependence is probably not a permanent feature of

any growth, for no method of endocrine therapy causes more than a temporary remission in the disease, at least when it has reached an advanced stage. After a variable time the growth becomes autonomous or hormone-independent and can no longer be halted by hormonal measures.

Hormones are usually assumed to act on the cells of the tumour itself. The fact that lesions in different tissues may behave differently under the influence of endocrine therapy suggests the possibility that the treatment affects primarily the tissues among which the tumour grows. This aspect of the subject requires further study.

RESPONSE TO TREATMENT

Endocrine methods of treatment are usually reserved for patients whose lesions have passed beyond the bounds of conventional surgery (simple and radical mastectomy) and radiotherapy. Most of those who have been treated by endocrine methods have been in clinical stage IV although some have been in stage III.

Assessment of the patient

The response to treatment can usually be described in one of the following ways:

(1) *Remission* —Objective evidence of regression of major lesions. No progression. No new lesions.
(2) *Subjective improvement.*—Relief of pain and other symptoms. The disease may be arrested, but there is no objective regression
(3) *No change.*—Disease continues to progress at the previous rate
(4) *Acceleration* —Disease progresses more rapidly than before treatment

The assessment is made on clinical grounds, on x-ray changes and on laboratory data. The patients are usually seen at monthly intervals. It may be clear within a few days of the start of treatment that there is subjective improvement or deterioration, but objective evidence of change in the growth is rarely obvious for 2–3 months.

Subjective improvement

Subjective improvement is valued highly by the patient and may render treatment well worthwhile, even when there is no objective regression (Cade, 1958) The first indication of improvement is usually relief from the pain of bony metastases. This is often immediate after operations on the endocrine glands. A patient who previously required frequent injections of morphine may need no analgesics at all. This is followed by an improvement in general health, a sense of well-being, [illegible] acity for work and a return to [illegible] with cortisone and testosterone, [illegible] ving any specific effect on the disease

Objective improvement

Objective improvement is recognized by regression of lesions which can be observed and measured. Some may vanish completely. Those on the surface of the body can be charted and photographed (Fig 54). X-ray changes in bones and in the



(*a*)



(*b*)

Fig 54 —Recurrence of breast cancer on chest wall of postmenopausal patient; (*a*) before treatment, (*b*) after stilboestrol for 6 months.



(a)

FIG 55.—Metastatic deposit of breast cancer in greater trochanter; (a) before treatment, (b) one year after hypophysectomy



(b)

chest are best assessed by a radiologist who is unbiased by knowledge of the treatment which has been given or of the expected response. Changes in osseous lesions occur slowly and can rarely be detected at intervals of less than 3 months (Fig.55) It is usual for all the lesions in one patient to behave in the same way as a result of therapy. Occasionally, however, some may regress while others remain stationary or even advance.

Laboratory data are usually less helpful than clinical and radiographic findings, but they should be taken into account. A favourable response may improve the blood picture (Fig 56). The concentration of calcium in the blood and its excretion in the urine may return to normal levels. The serum alkaline phosphatase level may rise while re-ossification is taking place and fall again when it is complete. The erythrocyte sedimentation rate may fall, but it often remains high throughout the period of remission. Hormone assays provide information about the effects of treatment on the function of the endocrine glands, but give no indication of the clinical response.

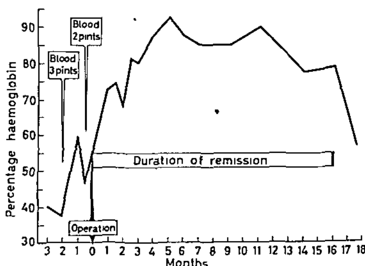


Fig. 56—Effects of hypophysectomy and eventual relapse on haemoglobin concentration in patient with widespread osseous metastases Five pints of blood were transfused *before* operation, but no other anti-anaemic treatment was given

Duration of response

The effects of treatment are temporary only The most effective methods cause remissions which last, as a rule, for 6–12 months (Fig. 57). Sometimes they are shorter and very rarely they persist for years. Those who respond to *treatment* survive, on the average, from 2 to 4 times as long as those who do not.

Factors which influence the response

Several factors have been found to influence the response to most forms of treatment.

The menopause

Women who are still menstruating respond much better to oophorectomy than those who have stopped. Oestrogens tend to accelerate growths in premenopausal

patients and to cause remissions in those past the menopause (either natural or induced). Testosterone, adrenalectomy and hypophysectomy are equally effective in both groups.

Length of time between primary treatment and re-appearance of the disease

Those patients in whom recurrent or metastatic lesions develop quickly (within 2 or 3 years) after treatment of the primary lesion are *less* likely to respond to endocrine therapy than those in whom metastases take several years to appear.

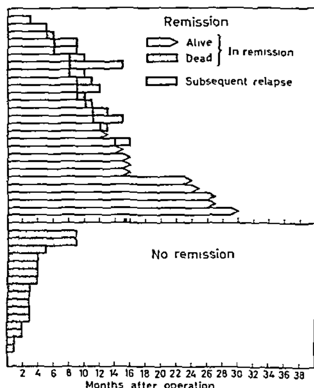


FIG 57—Duration of remission and survival in patients surviving hypophysectomy plus irradiation with yttrium-90 (Belfast series: C A Gleadhill and A. R Taylor) All patients underwent operation 12 months or more before the last assessment Twenty-six (62 per cent) had remissions. The average duration of remission was 13+ months and the average length of survival was 14+ months. All those who survived more than 16 months remained in remission Sixteen patients (38 per cent) had no remission. The average length of survival was 3½ months.

Site of lesion

No site precludes or ensures a remission, but lesions in some sites are more responsive than those in others. In general, metastases in the brain, the liver and the lungs carry a poor prognosis, while those in lymph nodes and bone are likely

gens are equally effective in both

Previous response to endocrine therapy

A temporary favourable response to one form of endocrine therapy renders a similar response to another more likely, but does not ensure it Conversely, a lack of response previously does not preclude a remission.

Other factors

The histological structure of the tumour does not affect the result. The age of the patient is unimportant, except in so far as it concerns the menopause.

Endocrine status

The aim of many workers is to discover methods which will enable them to recognize, by hormone assays, those patients who are likely to respond to particular forms of treatment. Several suggestive tests have been devised, but none is of proved value (Strong, 1958).

HORMONAL METHODS OF TREATMENT

Androgens

Rationale

Androgens may have two actions as follows: (1) inhibition of the production of gonadotrophins by the pituitary and hence of oestrogens and progesterone by the ovary, and (2) antagonism of the action of the ovarian hormones. They may also cause subjective improvement by increasing the appetite and encouraging the formation of protein.

Administration

Androgens may be administered in three ways.

Intramuscular injections.—Testosterone propionate in oil is given by intramuscular injection 3 times a week The dose is 25–100 milligrams.

Sub-lingual therapy—Methyl testosterone, 50 – 100 milligrams per day, can be absorbed from the mouth and inactivation by the liver is thereby avoided It is a convenient but expensive form of therapy.

Oral treatment.—Fluoxymesterone is given orally, in tablets, in a dose of 20 [illegible]

drawn if they cause untoward effects.

Results

About half the patients obtain some benefit. Objective remissions are observed in about 20 per cent both before and after the menopause, and subjective improvement occurs in another 30 per cent (Pyrah, 1956). Bony lesions respond well at all ages. Soft tissue lesions are affected more in premenopausal than in postmenopausal patients.

Disadvantages

Treatment with androgens may have severe drawbacks.

(1) *Amenorrhoea is inevitable and frank virilization is not uncommon.* The so-called "non-virilizing androgens" are being used extensively with good results in some patients (van der Werff, 1958), but they have not yet been shown to be so

effective as the ordinary preparations; nor are they entirely free from virilizing effects.

(2) Fluid retention may be dangerous in patients with cardiovascular disease.

(3) Androgens may, though rarely, accelerate growth of the tumour, possibly by being converted in part into oestrogens in the body.

(4) Hypercalcaemia may develop if growth is accelerated. It causes nausea, vomiting, diarrhoea, weakness, apathy, renal damage and peripheral circulatory failure, which may prove fatal.

Oestrogens

Rationale

It seems irrational to use oestrogens, which are known to stimulate tumour growth, to treat the disease. They may, however, have three actions. (1) Inhibition of some aspects of pituitary function, particularly when given in massive doses (Kennedy, 1957) Small amounts of oestrogen support normal development of the breast, while large amounts inhibit it. (2) An antimitotic action which affects the tumour directly. (3) Encouragement of hyperplasia and sclerosis of elastic tissue, which may enhance the reparative action of the stroma surrounding the tumour cells (Emerson and his colleagues, 1953). Evidence in support of a local action (either action 2 or 3 above) is provided by a patient whose tumour regressed during oestrogen treatment after failing to respond to total hypophysectomy.

Administration

Two forms of oestrogen therapy may be used.

Oral therapy.—Stilboestrol is given in tablet form The initial dose is 5 milligrams 3 times a day. This may be increased up to 100 milligrams a day if it is tolerated by the patient Nausea and vomiting are common and can be avoided to some extent by the use of enteric-coated capsules. Ethinyloestradiol, 0·2 milligrams, initially 3 times a day, is less irritating, but more expensive.

Intra-muscular injections.—Oestradiol monobenzoate or oestradiol dipropionate, 20 milligrams of either initially, is given 3 times a week by intramuscular injection. These drugs are sometimes valuable when the oral route is not tolerated.

Results

In those patients past the menopause 25–30 per cent obtain remissions (Pyrah, 1956). Oestrogens cause more improvement in soft-tissue lesions than in osseous ones (Nathanson, 1952). They should not be used in women who are still menstruating, since they commonly lead to acceleration of tumour growth.

Disadvantages

Nausea and vomiting are common and have been mentioned already. Fluid retention, uterine bleeding and pigmentation of the areolae and axillae may occur. The patient should be warned to expect uterine bleeding for a few days when the treatment is stopped.

Progesterone

Progesterone produced remission in only 2 patients out of 20 who were treated (Gordon and his colleagues, 1952). It is not advised.

Adrenal steroids

Rationale

The secretion of oestrogens and of androgens by the adrenal cortex is under the control of corticotrophin (ACTH), the production of which is inhibited by large doses of cortisone The secretion of ovarian hormones is under the control of gonadotrophins, the secretion of which is increased by adrenal steroids. It is therefore irrational to use them unless the ovaries have been removed, even in patients who have passed the menopause.

Administration

Cortisone acetate is given in tablet form by mouth. The usual dose is 100 milligrams 3 times a day, smaller doses are ineffective (West and his colleagues, 1954) An intramuscular preparation is also available. When cortisone therapy is to be stopped the dosage must be reduced gradually over a period of about 2 weeks. Prednisone, an analogue of cortisone, may also be used in one-quarter of the dosage

Results

A sense of well-being follows frequently and inhibition of inflammatory reactions may cause [illegible] of tumours Objective remissions [illegible] per cent of patients. T[illegible], that which follows the use of sex hormones or of glandular ablation.

Disadvantages

The high doses which are required are liable to produce severe metabolic derangements. All the signs of Cushing's syndrome, gastro-duodenal ulceration and pathological fractures may develop. The fluid and the electrolyte disturbances are less marked with prednisone than with cortisone The changes are all reversible Acute adrenal insufficiency may follow the too rapid withdrawal of the drug.

Thyroid hormones

Rationale

There is some evidence of a causal relationship between hypothyroidism on the one hand and the development and progression of breast cancer on the other Thyroid function is frequently depressed in those patients who have blood-borne metastases (Edelstyn, Lyons and Welbourn, 1958). It is interesting to note that the first patient on whom Beatson (1896) performed an oophorectomy was given thyroid extract also.

Administration and results

Preliminary reports only are available. Desiccated thyroid, 120–180 milligrams per day by mouth, may reduce the likelihood of metastases developing after mastectomy and cause regression of established lesions (Loeser, 1954, 1958) The same preparation, in doses of 60 to 120 milligrams per day and combined with cortisone, may cause regression in 50 per cent of patients (Lemon, 1955, 1957).

The remissions are said to last longer than those produced by adrenal steroids alone. A controlled therapeutic trial of the effectiveness of thyroid extract as a prophylactic measure against the development of metastases is being conducted in Northern Ireland (Edelstyn, Lyons and Welbourn, 1958). No effect has been observed after 2 years

Disadvantages

Signs of hyperthyroidism are not as common as might be expected, presumably because patients with blood-borne metastases tend to have reduced thyroid function If they develop, the dose must be reduced.

SURGICAL METHODS OF TREATMENT

Oophorectomy

Rationale

The ovaries are the main source of oestrogens and of progesterone in women of child-bearing age and a subsidiary source in those past the menopause. Since many tumours are oestrogen-dependent, and some possibly progesterone-dependent, removal of the ovaries should be of benefit, at least in younger women.

Method

Surgical excision is the method of choice. The operative mortality is extremely low except in those women who are acutely ill. The whole uterine adnexa should be removed, and not the ovaries alone, since they contain ovarian hilus cells which can possibly secrete oestrogens (Morris and Scully, 1958) Irradiation is an unreliable method of destroying the ovaries and is not advised (Kennedy, 1957; Treves and Finkbeiner, 1958).

Effects

As a therapeutic measure, oophorectomy causes objective remission in 40–50 per cent of women before the menopause but in only 10–15 per cent after (Lett. 1905; Treves and Finkbeiner, 1958). Rarely it causes acceleration of the growth (Wilson, Jessiman and Moore, 1958).

Oophorectomy is sometimes undertaken as a prophylactic measure at the time of mastectomy Few series have been reported (Horsley, 1947; Smith and Smith, 1953; Treves, 1957; Treves and Holleb, 1958), but it would appear that the procedure almost halves the recurrence rate at all periods after operation, especially in patients with axillary metastases The effect is not, apparently, confined to premenopausal women. This matter deserves more thorough investigation

Adrenalectomy plus oophorectomy

Rationale

The adrenal cortices are the main source of oestrogens, progesterone and androgens in women whose ovaries have been removed or in those who have passed the menopause. It is irrational to remove the adrenals without the ovaries, since even in older women the latter often continue to secrete

Method

The adrenals are usually removed through lumbar incisions and the whole operation (including oophorectomy) done in one, two or even three stages (Cade, 1955). Alternative techniques have been described, which allow both adrenals to be removed without turning the patient. An anterior (Aird and Helman, 1955) or two posterior (Lapides, 1958) incisions may be used. Large doses of cortisone are needed over the period of operation and a maintenance dose of 25–75 milligrams per day is required indefinitely. Great care is required in the immediate and remote post-operative periods to prevent adrenal insufficiency, which can appear suddenly and be fatal (Welbourn, 1957; Franksson, 1958) Hydrocortisone hemi-succinate, which acts very rapidly, is used for the treatment of an adrenal crisis; 100 milligrams, injected intravenously, takes effect rapidly and can be followed by cortisone intramuscularly or by mouth.

Results

The operative mortality varies from about 2–10 per cent. If the procedure is undertaken in staged operations a variable number of patients die before it is completed. Objective remissions are found in 30–50 per cent of all patients and subjective improvement in another 20 per cent (Cade, 1958; Hellstrom and Franksson, 1958; Pyrah, 1958). Improvement sometimes follows removal of one adrenal Rarely adrenalectomy causes acceleration of the growth (Wilson, Jessiman and Moore, 1958) Adrenalectomy plus orchidectomy is sometimes effective in carcinoma of the male breast (Pyrah, 1956).

Disadvantages

The operation is formidible and involves 2 or 3 incisions, if not 2 or 3 stages. The operative mortality is not negligible Life after operation is entirely dependent on cortisone substitution therapy and is relatively precarious.

Hypophysectomy and pituitary destruction

Rationale

The anterior pituitary produces gonadotrophins, which control the secretions of the ovary, corticotrophin (ACTH), which regulates the adrenal cortex, prolactin and growth hormone. Corticotrophin also controls the activity of ectopic adrenal tissue which may continue to function after adrenalectomy (Graham, 1953) Hypophysectomy should therefore, at one operation, prevent the secretion of all the known hormones which may promote tumour growth.

Methods

Surgical hypophysectomy requires a skilled neurosurgical team. Even in the best hands total removal of the pituitary is not always achieved. Many different methods have been devised to render its removal or destruction simpler or more complete. The following are the more important procedures:

(1) *Standard operation.*—Formal craniotomy and surgical excision is the usual method. The technique is described by Falconer (Atkins and his colleagues, 1957) and by Radley Smith (Baron, Gurling and Smith, 1958)

(2) *Attempts to simplify the procedure*

(*a*) Craniotomy with simple division of pituitary stalk, implantation of radioactive material into the pituitary, or a combination of the two (Rothenberg and his colleagues, 1955, Buxton and his colleagues, 1958)

(*b*) Transnasal approach with insertion of radioactive material (Forrest, Blair and Valentine, 1958; Forrest and his colleagues, 1958; Fraser and his colleagues, 1959). Yttrium-90 is more effective and safer than radon.

(*c*) External irradiation with 340 MeV proton beam (Lawrence and Tobias, 1956)

(3) *Attempts to ensure complete pituitary destruction*

Craniotomy with implantation of radioactive material after surgical hypophysectomy:

(*a*) Gold-198 in fibrin foam (Baron, Gurling and Smith, 1958).

(*b*) Yttrium-90 in dental wax (Edelstyn and his colleagues, 1958; Gleadhill, 1958).

After all these procedures, permanent oral replacement therapy is required Cortisone (25–50 milligrams per day), which has some electrocorticoid effect, is the steroid of choice. The adrenal cortex may continue to secrete aldosterone after hypophysectomy, but patients who are maintained on prednisone or similar "pure" glucocorticoids occasionally develop salt deficiency. Thyroid extract (120 milligrams dried thyroid per day) is required after the first month. Diabetes insipidus frequently follows these operations and may be permanent Its severity appears to be greatest when the pituitary stalk is divided at a high level. It can be controlled with posterior pituitary extract (either as snuff or as injections of pitressin tannate, 5–10 pressor units, from twice daily to twice weekly as required)

Extent of pituitary destruction

It is not yet known whether complete removal or destruction of the pituitary is necessary for the production of either complete functional depression or an optimal therapeutic effect Remissions may follow incomplete destruction and failure may follow complete removal

The study of serial sections of the pituitary fossa after death is the only certain method of estimating the extent of destruction. After surgical hypophysectomy, histologically normal cells remain in most cases and up to 10 per cent of the gland may be left behind (Falconer, 1957; Luft and his colleagues, 1958). All the "simpler" methods of pituitary destruction are probably still less effective. Preliminary reports suggest that the combination of surgical removal and intrasellar irradiation of the fossa may be the best method available, but even this does not produce complete destruction in every case.

During life pituitary function may be measured directly by assay of the excretion of gonadotrophins in the urine and indirectly by assessment of the function of the thyroid, the adrenals and the ovaries (Pearson and Ray, 1958). All these methods

is discussed below.

The problem is complicated by the fact that anterior pituitary tissue is found constantly in man in the region of the nasopharynx (Boyd, 1956; Müller, 1958). It is not known whether this "pharyngeal pituitary" has any function and no method has been devised for its destruction.

Results

Following surgical hypophysectomy the operative mortality varies in different series from nil to 20 per cent. Objective remission follows in from 30–65 per cent of patients (Fig 57) and subjective improvement or arrest of the disease in a further 10–15 per cent (Atkins and his colleagues, 1957; Kennedy, French and Peyton, 1956; Forrest and his colleagues, 1958; Edelstyn and his colleagues, 1958; Baron, Gurling and Smith, 1958; Luft and his colleagues, 1958; Ray and Pearson, 1958; Pearson and Ray, 1959). The operation usually causes slight personality changes, which consist of an improvement in mood, and decreased aggressiveness and libido (Schon, 1958)

Following transnasal implantations of yttrium 90 the operative mortality is about 5 per cent in experienced hands (Forrest and his colleagues, 1958), but probably much higher in the hands of those who have not made a special study of the technique. The objective remission rate is about 25 per cent. Hypophysectomy is sometimes effective in carcinoma of the male breast (Luft and his colleagues, 1958).

Disadvantages

The operative mortality is not negligible. Partial blindness, damage to the second and third cranial nerves, cerebrospinal rhinorrhoea and meningitis are the main complications, but are uncommon. The nervous lesions may be caused by radiation as well as by surgical trauma. They can be minimized by using a *beta*-ray emitter, such as yttrium-90, rather than a source of *gamma*-rays, such as radon, and by screening the radioactive material with muscle or fibrin foam. Replacement therapy is essential, but the ill-effects of stopping corticosteroids for short periods are less serious than they are after adrenalectomy. The injections which may be required for the control of diabetes insipidus are an inconvenience.

Comparison between adrenalectomy plus oophorectomy and hypophysectomy

It is not yet certain which of the two procedures has the more to offer. The evidence is as follows

(1) Hypophysectomy probably carries a slightly higher mortality rate, but is [illegible]

benefits of the operation. Transnasal implantation of yttrium-90 is a comparatively trivial procedure which can be used on patients who are too ill to undergo major operations.

(2) The reported remission rates following hypophysectomy are, on the whole, slightly higher than those following adrenalectomy plus oophorectomy. In Northern Ireland the remission rate in those who survive operation is nearly twice as high after

hypophysectomy (plus intrasellar irradiation with yttrium-90) as after adrenalectomy plus oophorectomy.

	Number of patients assessed	*Objective remission*
Hypophysectomy plus yttrium-90	42	26 (62 per cent)
Adrenalectomy plus oophorectomy	21	7 (33 per cent)

(χ^2 = 4·5 Probability of difference being due to chance is between 1 in 20 and 1 in 50.)

(3) The quickest method of providing a precise answer to the question is that of the controlled clinical trial. Reports of two only have been found In the Guy's-Maudsley series the results are inconclusive but tend to favour hypophysectomy (Atkins and his colleagues, 1957; Atkins, 1958). In Glasgow no difference has been found between the effects of yttrium 90 insertion (transnasal) and adrenalectomy plus oophorectomy (Forrest and his colleagues, 1958).

(4) In most cases hypophysectomy has produced no benefit in patients who have previously failed to respond to adrenalectomy plus oophorectomy (Baron, Gurling and Smith, 1958; Ray and Pearson, 1958; Luft and his colleagues, 1958; Forrest and his colleagues, 1958). Remissions have, however, followed in a few. In one case adrenalectomy failed to produce a remission after hypophysectomy (Ray and Pearson, 1958)

The evidence suggests that, in competent hands, surgical hypophysectomy is probably the better procedure

Excretion of oestrogens and response to operation

If removal of oestrogens from the body is the sole means by which these surgical procedures cause benefit it should be possible to correlate the excretion of oestro- [illegible]

patients who have undergone oophorectomy and adrenalectomy, but the results are more promising after hypophysectomy. The effects of the operations on oestrogen excretion are variable. Oophorectomy regularly reduces it in premenopausal women, but in those past the menopause the operation has no consistent effect. Subsequent adrenalectomy reduces it still further. Hypophysectomy usually abolishes the excretion of oestrogens, but some patients continue to excrete small, or even large, quantities intermittently or continuously. Remissions may proceed in those who continue to excrete oestrogens and the disease may advance in those who excrete none. The problem is not simple and requires further study.

A POLICY FOR THE TREATMENT OF PATIENTS WITH ADVANCED CANCER OF THE BREAST

No final conclusions are possible about the best course to adopt in the treatment of any individual patient and the policy which is outlined here is tentative only. The most effective measures are the most drastic and one is often reluctant to advise them in a patient who is still relatively fit. On the other hand, if they are withheld for too long the patient may deteriorate rapidly and reach a stage at which she

is too ill to undergo major surgery with safety. It must be remembered that two-thirds of the patients at the most will receive real benefit from any procedure, that the average duration of remission is 6–12 months and that only a very few patients will survive for as long as 3 or 4 years.

I. Patients unsuitable for mastectomy and radiotherapy, but who are still relatively fit

Premenopausal

(1) Oophorectomy is the treatment of choice. It is simple, safe and effective in nearly half of the patients so treated.

(2) Androgens are less effective and have serious disadvantages. They should be reserved for those patients who are unsuitable for operation.

Postmenopausal

(1) Oestrogens are worthy of trial, especially if the disease is localized to the region of the breast or to other soft tissues.

(2) Androgens are preferable if osseous lesions predominate.

II. Patients in whom the disease is advancing rapidly or who have failed to respond to these measures

(1) Surgical hypophysectomy is the method of choice if facilities are available.

(2) Transnasal implantation of yttrium-90 may be used if surgical hypophysectomy is not available or if the patient is too ill for it.

(3) Adrenalectomy plus oophorectomy is advised if (1) and (2) are not practicable.

(4) Androgens or oestrogens (as in I) may be used if the patient is too ill for surgery.

III. Patients who fail to respond to these surgical procedures or who relapse after an initial remission

The outlook is practically hopeless, but oestrogens, prednisone and thyroid extr[illegible]
has [illegible]
bony lesions can often be obtained from palliative radiotherapy. Strong [illegible] and tranquillizers are helpful in the terminal stages.

CARCINOMA OF THE BREAST AND PREGNANCY

Carcinoma of the breast usually runs a highly malignant course if it coincides with pregnancy or lactation, and it is often recognized only at a late stage of the disease (White, 1954) Treatment should be undertaken as early as possible. Therapeutic abortion does not confer any benefit. If the disease is advanced the problem is difficult. Oophorectomy causes abortion in the first trimester but not later. Androgens may cause virilization of the foetus (Moncrieff, 1958). Hypophysectomy, followed by normal labour and regression of metastases, has been described (Little and his colleagues, 1958). Pregnancy following the primary treatment of breast cancer does not appear to affect the prognosis adversely.

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ABSTRACTS RELATING TO THE BREAST

ENDOCRINE ASPECTS

Hormone-dependent breast cancer

[illegible] ...cancers are spheroidal- ...n constitutes the major ...lignancy is determined ...is put forward that the

mammary response. Lack of the growth response to oestrogen and progesterone therapy is attributed to lack of a mammotrophic pituitary hormone. In cases of breast cancer

about a year before the onset of the menopause. The regression may be due to a natural

establish whether a favourable prognosis can be correlated with the detection of a reduced urinary output of gonadotrophin

Tumour autonomy in breast cancer

Recognition of the hormone-stimulated tumour

the rate of growth of the disease. Forty years ago, when ovariectomy was the sole method of surgical treatment, it would have been postulated that the tumour had passed into an autonomous growth phase, but with modern techniques it was shown that the tumour was still responsive to hormonal therapy. In the study of another patient with mammary cancer and bone metastases it might have been inferred on two occasions that the neoplasm had ceased to be hormone stimulated and had become autonomous. After

Hormone assay

STRONG (1958) believes that many hormones may play a part in the problem of breast cancer. Hence in the investigation of the disease hormone assays must inevitably be elaborate. Assays of sex hormones in the premenopausal patient are likely to be valueless unless the tests extend throughout a complete menstrual cycle. At present oestrone, oestradiol-17β, oestriol and pregnanediol are the only products of ovarian activity in the urine which can be measured reliably. It is true that the urine contains numerous excretion products of the hormones of the adrenal cortex, but the relation between the adrenal cortex and the behaviour of mammary cancer has not been defined in terms of specific hormones. The adrenal 17-oxosteroid, 11β-hydroxyaetiocholanolone, is often found in the urine in cases of breast cancer, and specific assay for compounds of this type may prove to be more helpful than the estimation of a group of metabolites. Hormone assays are of value not only in deciding upon the most suitable form of treatment but also in determining the effect of treatment. For example, studies of oestrogen excretion are regarded as appropriate after hypophysectomy, oophorectomy and adrenalectomy [illegible] remission of the disease. The [illegible] phins [illegible] out assays of urinary oestrogens in 7 cases of breast cancer affecting patients in the post-menopausal phase. In most cases the excretion of oestrogen was about 5 times more than normal. After treatment with cortisone 3 of [illegible] in the urine. Investigating a larger group [illegible] found that, during treatment with cortison [illegible] trophin and prolactin. Subsequently Lemon and his colleagues administered cortisone and a thyroid preparation to patients with breast cancer. Urine tests revealed an increase in gonadotrophins, but in 75 per cent of cases there was a reduction in the amount of oestrogens, androsterone and aetiocholanolone.

Effect of oophorectomy

[illegible] able regression of the mammary tumour. An objective remission was observed [illegible] 143 patients who were still menstruating. The remission persisted for an average period of approximately 14 months. No correlation was established between the response and the histological grading of the neoplasm, but a reduced response was encountered in cases of intra-abdominal metastases, especially when the liver was affected. A relatively high remission rate was obtained when mastectomy was performed more than 2 years before surgical castration. The post-operative mortality was 2 6 per cent, with 3 deaths due to advanced pulmonary disease and 2 deaths due to severe hypercalcaemia. Decrease in hypercalcaemia and hypercalcuria was not regarded as objective evidence of tumour [illegible] osseous lesions. Oophorec- [illegible] urrent or metastatic cancer [illegible]

performed after the menopause. The operation is indicated, however, [illegible] radical means. Vaginal smear [illegible] ould [illegible] uch [illegible] The is sufficient to produce a urinary output in excess of 2,000 3,000 [illegible] authors draw attention to the data concerning a series of cases which were analysed by

Lett in 1905. Bilateral oophorectomy was performed on 99 patients with inoperable mammary cancer. Improvement was observed in 41 per cent of patients under the age of 50 years Four patients survived for 4½ years.

Correlation of clinical results with oestrogen production

BULBROOK and his colleagues (1958a) attempt to correlate the fluctuations in urinary oestrogens with the clinical consequences of oophorectomy in cases of breast cancer. The authors selected a group of 24 women with a history of regular menstruation prior to the operation. In this group progressive metastatic cancer developed after oophorectomy Oestrogen tests were performed on 230 specimens of urine A study of the results indicated that oophorectomy had removed a major source of oestrogen production. There was an invariable reduction in the amount of urinary oestrogen. Adrenal secretion of oestrogen was always detectable, but with wide limits of variation The case is recorded [illegible]

than 1 year before oophorectomy the amount and pattern of excreted oestrogen showed no difference from the findings in the premenopausal group. In postmenopausal cases [illegible]

and adrenal glands It would appear that the clinical success of oophorectomy in some premenopausal cases may depend either upon the extent of the postoperative decrease in eostrogen production or upon a decrease in circulating oestrogen below a critical level irrespective of the level prior to the operation

Adrenalectomy

Correlation of clinical results with oestrogen production

[illegible]

excretion or with a negligible and spasmodic excretion of the hormone. Five patients derived no benefit from adrenalectomy and the remaining patients excreted oestrogen while the disease was progressing. In general, continued excretion of oestrogen was more [illegible]

disease but with no evidence of urinary oestrogen.

Hypophysectomy

Correlation of clinical results with oestrogen production

In a discussion on the effect of hypophysectomy upon 16 cases of breast cancer, BULBROOK and his colleagues (1958b) give an account of urinary oestrogen estimations which were made before and after the operation One man and 4 women derived no benefit from the operation These patients showed evidence of progressive skeletal metastases. In the case of the male patient hypophysectomy reduced oestrogen excretion, but among the female patients the mean post-operative level of oestrogen excretion was higher than the pre-operative level. Objective remission of growth was induced in 11 women and for the most part oestrogen excretion was absent from the urine in this group.

It is noteworthy, however, that the patients showed a relatively low pre-operative level of urinary oestrogen. In 9 cases the mean levels were lower than those found in 39 women with metastatic breast cancer after the natural menopause or after bilateral oophorectomy A woman, aged 65 years, showed evidence of urinary oestrogen for a period of 12–18 days after hypophysectomy, but *no oestrogen could be detected subsequent to this period.* Apparently 2 weeks may elapse before the circulating pituitary and adrenal hormones are eliminated.

Effect of hypophysectomy

average period of 10·1 months. Among patients who showed no response to treatment life was prolonged for an average period of only 3·2 months. It was rarely possible to remove the anterior pituitary tissue completely, but clinical improvement occurred even when 10–20 per cent of the tissue remained in the fossa. There was little evidence of regrowth of either the pituitary stalk or the gland parenchyma. In many patients there was considerable post-operative improvement in the haemoglobin level. Sometimes the plasma-protein levels became normal and paper electrophoretic studies revealed an increase in albumin and a decrease in α_2-globulin. Owing to the abolition of thyroid-

... Thyroid extract was adminis-

... *ired thyroid function.* Limited

... ormed in a few cases, but it was found that a relatively large amount of pituitary tissue had survived after the operation. The authors believe that ablation of the pituitary gland is best achieved by surgical hypophysectomy combined with the insertion of unscreened ^{198}Au or ^{90}Y seeds in a dosage of 15 millicuries. The bulk of the pituitary gland is removed, the pituitary stalk is divided and the superior hypophysial arteries are interrupted. Hypophysectomy, in preference to adrenalectomy, is regarded as an effective method of palliation in advanced cases of cancer of the breast.

Hypophysectomy combined with intrasellar irradiation

... (1958) draw attention to the fact that neither surgical ... the pituitary regularly causes complete destruction of ... ed *the effect of combining the two procedures* in 25 ... The operation was performed through the right ... a was packed

in only 1 case. Five deaths occurred within 5 days of the operation At necropsy 1 fossa was observed to be empty and 2 fossae contained small fragments of pituitary tissue.

Screw-implantation of the pituitary

Yttrium-90

Forrest, Blair and Valentine (1958) describe their latest technique of implanting yttrium-90 into the pituitary gland It is designed to allow accurate placing of the sources of irradiation and to plug the communications between the pituitary fossa and the nasopharynx. A cylindrical rod of yttrium oxide is encased in a nylon sheath, activated in the Harwell pile, Bepo, and fitted into a stainless steel orthopaedic screw. Part of the screw accommodates a loosely fitting screwdriver. By means of a director apparatus cannulas are inserted into the nostrils as far as the outer wall of the pituitary fossa. A diamond-

and in each case the pituitary gland was found to have been almost entirely destroyed. Complete destruction of the gland was observed at necropsy on a patient who died 6 weeks after implantation.

Thyroid function

Edelstyn, Lyons and Welbourn (1958) report on a study of the thyroid function of 67 patients with mammary cancer. The series was divided into two groups according to the clinical and radiological findings In the first group the tumour was confined to the breast, chest wall or local lymphatic nodes and in the second group there was evidence

was determined with a ring counter. A study of the data revealed that the thyroid function was lower in patients with blood-borne metastases than in those with local disease. In a discussion on the findings the authors point out that it is not clear whether blood-borne metastases depress thyroid activity or whether reduced thyroid function favours the distant spread of malignancy.

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THE SURGICAL TREATMENT OF RUPTURED INTRACRANIAL ANEURYSM

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INTRODUCTION

Since Symonds in 1923 drew attention to ruptured intracranial aneurysm as the commonest cause of subarachnoid haemorrhage, the problem of prevention of further rupture has been extensively studied. A landmark for this type of surgery was the description by Moniz (1927) of the technique of cerebral arteriography. The names of Dott (1933), Jefferson (1937) and McConnell (1937) in Britain are remembered as early workers in this field; along with these must be coupled the name of Dandy (1944) in the U.S.A who did so much without the aid of arteriography. In recent times Falconer (1950, 1951), Norlén and Olivecrona (1953), *McKissock and Walsh (1956)* and Logue *(1956)* have added to our understanding of the subject. Potter (1956) gave a well-balanced account illustrated by beautiful *arteriograms.*

Frequency

Rupture of an intracranial aneurysm occurs with some frequency. In the Swansea [illegible] 450 in-patients per annum, [illegible] 58. *These figures do* [illegible] nts admitted to the neurological and general medical services. The maximum incidence is in the 35–55 years age group. The diagnosis and differential diagnosis of intracranial bleeding from a ruptured intracranial aneurysm has been dealt with by *Potter* (1956).

Pathology

Gillingham (1958) has described in some detail the pathology of these aneurysms and their rupture. He points out that approximately 50 per cent rupture at some time or other into the brain substance and occasionally into the ventricular system as well. Aneurysms of the anterior communicating and middle cerebral arteries

are particularly liable to rupture into the brain. Other aneurysms, like those at the posterior communicating-internal carotid junction and at the termination of the basilar artery, lie free within the basal cisterns, and, therefore, tend to bleed directly into the subarachnoid space. At times continued intracerebral bleeding may result in extravasation into the ventricles. Again, blood may find its way along the fissures of the brain and form a collection in the subdural space. He points out that extravasation of blood into the basal cisterns and over the cerebral cortex inevitably causes some obstruction to the cerebrospinal fluid circulation There follows distension of the ventricular system and, to some extent, of the basal cisterns. This may be usefully exploited at operation, for when the ventricles are punctured and drainage instituted, a marked reduction of intracranial tension ensues, facilitating approach to the aneurysm with a minimum amount of brain retraction.

At the time of rupture of an aneurysm arterial spasm may occur in the artery near the neck of the sac Such spasm may be of long or short duration, and doubtless it exerts a beneficial effect on the arrest of haemorrhage in the acute stage, but the resulting ischaemia may result in grave neurological deficits. Spasm may be further aggravated by radio-opaque substances used in arteriography, or by manipulation of vessels at operation. Arterial spasm therefore has an important effect on morbidity and mortality. It is of particular importance in anterior communicating aneurysms because of the relation of these aneurysms to both anterior cerebral arteries and their striate branches. Arteriography attempted while spasm is present may not show an aneurysm; but if repeated some days later when spasm has relaxed, the aneurysmal sac will frequently be demonstrated. Because of this tendency to spasm during operative manipulation Gillingham applies papaverine solution (2·5 per cent) on lintine swabs to the vessel walls. He has found this to be an excellent prophylactic against spasm, and moreover the solution will often relax vessels already in spasm.

Clinical considerations

In any case of ruptured aneurysm in which surgical treatment is contemplated careful consideration has to be given to the following factors.

Evidence of previous subarachnoid haemorrhage

It is always important to ask a patient or his relatives about any past episodes of severe headache and neck stiffness, as frequently evidence of previous minor leaks is found Very often a massive haemorrhage is preceded by one or two minor episodes which are wrongly labelled fibrositis or rheumatism and which clear rapidly in 3 or 4 days. It is always difficult to decide whether to operate upon an aneurysm which has apparently bled for the first time if the patient has no neurological disability and is apparently well on the way to recovery. Evidence of minor leaks within the preceding months is an indication for active surgical treatment.

The clinical condition of the patient

On admission following rupture of an aneurysm a patient may be in any stage between full consciousness and deep coma. In addition there may, or may not, be focal neurological signs. There may be merely an isolated oculomotor palsy with

severe headache, or signs of raised intracranial pressure secondary to intracerebral haematoma formation. The problem may be further complicated by the occurrence of repeated haemorrhages within a short period resulting in rapid deterioration of consciousness. With such variation in the clinical picture it is extremely difficult to formulate any hard and fast rule regarding arteriographic investigation and operative treatment.

The time interval which has elapsed between rupture and admission to the neurosurgical unit

This is intimately bound up with the occurrence or persistence of spasm in the vessels and so with the optimum time for arteriography and operation.

The position of the aneurysm in relation to the circle of Willis and its branches

Pathological surveys have shown that approximately 75 per cent of ruptured aneurysms occur on the anterior half of the circle of Willis or its branches, and therefore, provided they are of sufficient size, they ought to be visible on good arteriograms. However, in practice by no means all of these aneurysms are demonstrated—probably because some are small. A few aneurysms are situated on the vertebral-basilar system of vessels; in Gillingham's series (1958) of 80 aneurysms treated by operation, only 5 occurred in this system. If bilateral (carotid) arteriography fails to demonstrate an aneurysm, then vertebral arteriography should be performed as occasionally an aneurysm may be shown on the posterior inferior cerebellar artery which can be treated successfully at operation.

Walton (1956) has shown that the mortality of patients with ruptured aneurysm treated expectantly within the first 8 weeks is in the region of 50 per cent, and that a further 20 per cent will die during the following 6 months from a further haemorrhage. About 15 per cent die within the first 24 hours of an initial overwhelming haemorrhage and surgery has little to offer (Walton, 1956). Gillingham (1958) believes that this figure of 15 per cent may be high and he points out that the first minor attack may frequently be missed. The second and often severe attack is frequently regarded as the first. He stated that after minor leaks the patient is relatively undisturbed and operating conditions within the initial few days are nearly ideal Intracranial pressure is almost normal and the brain is slack and more easily retracted. Mortality and morbidity from operative treatment in the conscious group with small extravasations is low. Mortality and morbidity from operative treatment in patients with altered consciousness and severe neurological deficit is high It would appear that any attempt at operative cure must better the 50 per cent mortality which occurs in the first 8 weeks.

ANEURYSMS OF THE INTRACRANIAL INTERNAL CAROTID ARTERY

This group of aneurysms comprises those arising at the internal carotid bifurcation and those arising at the origin of the posterior communicating and anterior choroidal arteries. For many years it has been accepted practice to treat these aneurysms by proximal ligation of the common carotid artery and internal carotid

artery in the neck. This is usually carried out in stages, after adequate cross-circulation at the circle of Willis has been demonstrated by arteriography, and after direct compression of the internal carotid artery in the neck has produced no untoward effect. The operation is performed under local anaesthesia. There can be no question that this method of treatment has reduced the frequency of further haemorrhage in this group of aneurysms.

Alternatively, the aneurysm may be approached intracranially with the object of applying a silver clip to the neck of the aneurysm. While this means a major intracranial operation, successful occlusion of the neck excludes the aneurysm from the circulation and leaves the cerebral circulation intact. Under favourable circumstances it is possible to cure these patients and leave no neurological disability. At times, however, during manipulation of the vessel the aneurysm may rupture and the internal carotid artery will have to be clipped. This, while uncommon, is a very real hazard and it may occur despite the most gentle of manipulations.

Ligation of the carotid artery in the neck

Shenkin, Polakoff and Finneson (1958) believe that carotid ligation in the neck offers a high degree of protection against recurrent haemorrhage. They followed, for 6 months to 7·5 years, a series of 19 patients treated in this way. The average age of their patients was 47·5 years; 18 had had subarachnoid haemorrhage; 5 had had previous subarachnoid haemorrhages. The aneurysms were localized by arteriography performed on the average 12 days after bleeding and ligation was done on the average 14 days after haemorrhage. Of the 19 patients 18 survived; the death occurred in a man who was semi-comatose with a right hemiparesis. He developed a haematoma in the left frontal lobe of the brain which was not evacuated.

Of the 18 survivors 17 are well and economically useful; the other patient is hemiparetic and aphasic over 4 years after the ligation. Following the ligation 6 patients developed hemiparesis with or without aphasia; 3 of these patients recovered completely and 2 recovered sufficiently to work. These results in a small series are good, but the average period of follow-up is only 3·5 years.

It is clear that when patients are relatively stabilized and conscious after a subarachnoid haemorrhage from a ruptured internal carotid aneurysm, cervical ligation may be carried out with safety. In this series, and others, the only immediate mortalities encountered were in the desperately ill and comatose patients. Schorstein (1940) pointed out the dangers of carotid ligation in the presence of coma Shenkin, Polakoff and Finneson (1958) state that, in general, patients with aneurysms that have ruptured should not have definitive surgical procedures performed unless they are conscious, and if they are conscious, definitive surgery should be done as soon as possible lest they bleed again. Therefore the time interval between onset of bleeding and surgical intervention cannot be rigidly fixed They believe that any intracranial approach in the treatment of this type of aneurysm of necessity offers a greater likelihood of mortality and morbidity than the relatively simple procedure of cervical carotid ligation. They prefer to ligate

the common carotid artery in the first instance, and then after an interval the internal carotid artery.

Hardy and his colleagues (1958) studied 53 cases of intracranial aneurysm treated by carotid ligation in the neck, and 1 case of aneurysm of the cervical internal carotid artery treated by excision They have conducted a 1–13 year follow-up study. In these 54 patients the aneurysms were distributed as follows: internal carotid artery 22; middle cerebral artery 14; anterior communicating artery 7; anterior cerebral artery 4; posterior communicating artery 4; posterior cerebral artery 3. Some of these patients were suffering their second or third attack of subarachnoid haemorrhage. After ligation 4 patients developed hemiparesis—2 recovered after 2 and 10 days respectively; the other 2 made partial recoveries. Four patients had recurrent haemorrhages after ligation and 3 of them died. A total of 7 patients died after ligation of the carotid artery: 3 of recurrent haemorrhage, 2 from the primary haemorrhage, that is, they were not helped by the ligation; and 2 died of causes not related to rupture or ligation. Of the patients who developed paralysis after ligation, 3 had aneurysms distal to the internal carotid artery, and 1 was on the internal carotid artery. Of the patients 42 are working. Any recurrent symptoms since ligation have been mild and infrequent.

The operation performed is ligation of the common carotid artery in continuity using two ligatures. They conclude that carotid ligation in the neck is of value in the treatment of intracranial aneurysms, particularly those of the internal carotid artery.

While the subject of cervical carotid ligation is under consideration, the work of Harris and Udvarhelyi (1957) concerning aneurysms at the internal carotid-posterior communicating junction should be mentioned They used two methods of treatment mainly—66 patients had proximal ligation of the carotid arteries in the neck and 12 had operations for direct obliteration of the aneurysm. For this type of aneurysm they preferred the former method, but they stated a direct attack on the aneurysm is indicated (1) if there is no anastomotic circulation or only a poor one, (2) if the aneurysm should fill during the test of contralateral anastomotic circulation, (3) if trial occlusion of the vessels results in neurological changes

The technique they adopted was occlusion of the common carotid artery in the first instance, followed by ligation of the internal carotid artery 3 months later—but only if arteriography showed the aneurysm had not disappeared or had become very much smaller Before ligation of the common carotid artery the vessel was always occluded by a clamp for 30 minutes to ensure that there were no untoward effects from occlusion. Acting on the suggestion of Professor Dott (1953), they also applied a more stringent test during the trial period of occlusion. This consisted of the intravenous administration of Arfonad, whereby the systolic blood pressure is dropped 50 points; if there were no neurological signs after this the wall of the artery was stripped, producing a peri-arterial sympathectomy, and the vessel was ligated in continuity Using this technique 17 patients developed hemiparesis at an average time of 17 hours after the operation. There was full recovery from hemiparesis in 12 patients. Three patients developed severe hemiplegia after direct intracranial attack on the aneurysm. Seven of the patients died after proximal

ligation, and 1 had recurrent haemorrhage. In the 12 patients who had the direct operation there were no deaths, but 1 patient had a recurrent haemorrhage.

Gillingham (1958) believes that proximal ligation in the neck, in two stages, is the method of choice in this type of aneurysm, provided cross-circulation is proved by arteriography to be adequate. If cross-circulation is inadequate the direct attack has to be performed. There were 25 patients with aneurysm of the intracranial internal carotid artery in his series. 18 are alive, well and working; 5 are seriously disabled and 2 are dead. Of the 5 disabled patients, 1 showed considerable neurological deficit from the primary haemorrhage; 4 developed neurological deficits post-operatively—2 from rupture of the aneurysm during the direct operation and 2 from occlusion of the carotid vessels in the neck—this was considered to be due to spreading thrombosis. In a later series of 8 aneurysms of this type treated by proximal ligation all are alive and well and show no significant morbidity.

Direct approach to the aneurysm

Bjorkesten (1958) states that since 1952 the direct approach has been the method of choice in the Finnish Red Cross Hospital. The neck of the aneurysm is either clipped or tied with linen thread. If this is not possible the aneurysm is wrapped with hammered muscle or Gelfoam. Forty-six aneurysms in 44 patients were so treated He points out that operation at an early stage is considerably more dangerous than if it is performed later after the acute symptoms and signs of bleeding have subsided. On the other hand, a deferred operation increases the risk of recurrent haemorrhage during the period of waiting. He himself, however, has not had to worry unduly about this waiting period, as the majority of his patients came from other hospitals 2 weeks or more after the last attack of bleeding. Those cases which were seen immediately after an acute episode of subarachnoid haemorrhage were treated conservatively for 1–3 weeks. One of these patients had 3 recurrent haemorrhages during the waiting period. None of his patients died while awaiting surgery Four patients died post-operatively—a mortality of 9 per cent The patients were all operated on under general, intratracheal anaesthesia with controlled hypotension using Arfonad Of the 4 patients who died in hospital 2 suffered rupture of the aneurysm at operation, the haemorrhage in 1 case being arrested with muscle and in the other by clipping A third patient died on the eighth post-operative day from an extradural haematoma The fourth patient died from a pulmonary embolus on the fourteenth post-operative day There were 2 deaths later, one from status epilepticus and the other from a brain abscess secondary to a bone flap infection.

Two of the 40 survivors had post-operative hemiplegias One of these was owing to carotid thrombosis which developed on the evening of the day of operation. The patient had been well and moving all limbs in the afternoon This patient survived for 2 years with a hemiplegia and epilepsy and finally died in status epilepticus The second patient who developed a hemiplegia had 3 aneurysms clipped; the hemiplegia later resolved.

There were 6 post-operative hemipareses but these subsided fairly soon afterwards. One of these was the patient who subsequently died of a brain abscess. The

survivors were followed for a period of 3 months to 4·5 years. Of the 38 survivors, 21 made a complete recovery and are doing full work. Ten of the survivors have impaired working capacity owing to pre-operative paresis, aphasia or ophthalmoplegia. Three have impaired working capacity because of operative complications (paresis, epilepsy). Three others are unable to work fully because of other diseases. One patient is totally disabled because of pre-operative hemiplegia and aphasia. There was no total disability which could be attributed to operative complications.

When the results of direct attack are considered along with those following judicious proximal carotid ligation, it becomes clear that this group of intracranial [illegible] eminently amenable to operative treatment. Botterell and [illegible] patients with cerebral vascular disorders. Seventy-three [illegible] from ruptured cerebral aneurysms, and these were operated upon under [illegible]sthesia together with hypothermia There were 30 patients suffering from internal carotid aneurysms; 16 were operated on 1 week or more after the last haemorrhage with no deaths; 14 patients were operated upon within the first 7 days and in this group there were 5 deaths. All 25 survivors were classified by them as having excellent results (well with no neurological deficit). In an addendum to their paper they mention 16 further patients with ruptured internal carotid aneurysms treated in the same way; 12 were operated upon in the first 7 days with 2 deaths; 4 were operated upon after 7 days with no deaths. These are excellent results These authors precede the intracranial operation by isolation of the common carotid and vertebral arteries in the neck. Before the clip or ligature is applied to the aneurysmal neck the common carotid artery is occluded They have found that this diminishes tension in the sac and prevents the clip or ligature tearing the taut sac. They concluded that hypothermia and cervical artery occlusion have improved the surgical treatment of ruptured aneurysm.

MIDDLE CEREBRAL ARTERY ANEURYSMS

These commonly arise at the first primary branching of the artery in the lateral half of the Sylvian fissure Because of their situation, rupture is frequently complicated by intracerebral blood clots which give rise to gross neurological disabilities. The clots are usually found in the temporal lobes and occasionally in the frontal lobes; many are very large and result in rapid deterioration of the clinical state In such cases timely operation may prove to be life saving, but there may be gross residual neurological disability from primary brain damage at the time of rupture, the end result depends upon the amount of this and whether the right or left cerebral hemisphere is involved.

Because of the gross neurological disabilities which often follow primary rupture, this group of aneurysms was regarded with less enthusiasm than the internal carotid group But Norlén and Olivecrona (1953) reported their experience with 17 middle cerebral aneurysms, 13 of which were occluded intracranially and 4 wrapped with muscle. There was only 1 death in the series. Petit-Dutaillis and Pittman (1955) recorded their experience with 9 patients suffering from ruptured middle cerebral aneurysms. In 2 patients intracerebral clot only was removed;

these patients died after operation. The other 7 patients had the aneurysm attacked directly; 5 did well and 2 died. They concluded that in view of the reasonable accessibility of these aneurysms it was justifiable to attempt surgical eradication.

Gass, McGuire and Simmons (1958) operated upon 12 patients with ruptured middle cerebral aneurysms. There were 2 deaths The 10 survivors were all well post-operatively and neurologically intact—with the exception of 1 patient who had a mild degree of aphasia. Before operation this patient had been totally hemiplegic and aphasic Of the 2 patients who died, one was in coma at the time of operation; the second patient died because of a large temporal haematoma, the existence of which was not recognized at the time of operation. Both patients who died were operated upon within 7 days of the rupture. The authors consider it inadvisable to operate upon any patient with an aneurysm, whether of the middle cerebral artery or any other artery, who has not shown a capacity to recover from coma At operation they used an exceptionally large bone flap carried well down to the floor of the middle fossa. In addition, they employed complete spinal drainage together with hypotension and hypothermia.

In discussing middle cerebral artery aneurysm, Gillingham (1958) states that clot within the Sylvian fissure is often a guide to the aneurysmal sac, but it is a wise precaution to define the main trunk of the middle cerebral artery at the medial end of the Sylvian fissure before exposure of the sac is attempted. The application of papaverine solution to the exposed vessels is an essential and early step to prevent development of spasm Usually the neck of the sac in this type of aneurysm is broad and implicates one or two of the peripheral branches. Ligation or clipping of the neck of the sac may cause constriction of the peripheral branches and may lead to post-operative neurological, emotional or intellectual deficits from ischaemia owing to kinking or thrombosis. Gillingham has abandoned this kind of occlusion since 1954. He wraps the sac in sterile muslin gauze followed by a layer of temporal fascia. This results in a dense covering of fibrous tissue within a few weeks and has been found to be very satisfactory with minimal post-operative complications and no recurrence of bleeding

Gillingham treated 26 patients in this group, 18 in the first 21 days after rupture Only 1 patient died and this was due to recurrent bleeding from a breach in an arteriosclerotic plaque on the middle cerebral artery—the site of the original haemorrhage Mortality was very low, but morbidity was high. Of the 18 cases treated in the first 3 weeks, 7 were severely disabled, of 8 patients treated after 3 weeks, 4 were severely disabled. This disablement, however, is more likely to be due to the primary rupture than to any operative complication

Botterell and his colleagues (1958) operated on 14 patients with this type of aneurysm—10 within the first 7 days with 2 deaths Four patients were operated on 7 days or more after rupture with no deaths. Of the 12 survivors, 6 were adjudged to have excellent results (well, no neurological deficits); 3 were considered to have good results (persistent neurological deficit—not disabling); 3 were classified as having bad results (mentally retarded, dysphasic, major neurological deficits). All were operated upon with the aid of hypothermia and the carotid vessels were exposed in the neck as in the internal carotid aneurysms. The authors remark on

the high incidence of intracerebral clots and comment that operation and evacuation of the clot within 24–48 hours may be essential to survival.

It is open to question whether early ligation of the cervical carotid arteries is of much value in ruptured middle cerebral aneurysm. The patients are frequently very ill indeed, comatose or semi-comatose, hemiplegic or aphasic. Cervical ligation at this stage is undertaken at the worst possible time (Schorstein, 1940). It seems clear that direct operation is the method of choice—preferably using hypothermia. If gross neurological signs are due mainly to intracerebral haematoma formation, good recovery of hemiparesis and dysphasia may result from evacuation of the clot. In these cases the surgeon may well be forced to operate in the early stages after rupture because of rapid deterioration in the clinical state from accumulation of blood.

ANEURYSMS OF THE ANTERIOR COMMUNICATING ARTERY

These aneurysms are situated beneath the preoptic region of the hypothalamus and in the midst of its blood supply. Only rarely is it possible to demonstrate arteriographically or at operation a discrete neck to the sac. More commonly there is a diffuse dilatation, virtually a ballooned channel connecting the two anterior cerebral arteries Because of their situation rupture may lead to alteration in consciousness, apathy and incontinence, spasm of the anterior cerebral arteries and their branches may result in further ischaemia. Therefore the primary haemorrhage, if severe, may have produced gross brain damage with marked metabolic changes which may be permanent. Aneurysms in this situation tend to bleed repeatedly, and if it is possible to occlude or obliterate such an aneurysm following a minor leak then the outlook is good. In stuporose patients it is wiser to delay operation to see if any spontaneous improvement takes place. If and when the patient returns to a conscious state it is usually possible to assess if any gross intellectual or mental impairment has followed the initial rupture.

Direct exposure of the aneurysm necessitates rather more brain retraction than in other situations. As Gillingham (1958) pointed out, prolonged retraction of the frontal lobe necessarily results in traction on the important striate branches of the anterior and middle cerebral arteries with the danger of spasm and further reduction of blood flow. Temporary contralateral hemiparesis and a slow return to [illegible] However in [illegible]

[illegible]

aneurysm with improvement in general condition and of [illegible] it is possible to expose the aneurysm and obliterate it with silver clips or wrap it with muscle with most satisfactory results.

Dott (1953) believed that tension within such an aneurysmal sac is maintained and its rupture often determined by the force of the arterial jet from the major arterial trunk After arteriography it is frequently seen that an anterior communicating aneurysm fills mainly from one anterior cerebral artery. If there is an adequate cross circulation the occlusion of the appropriate anterior cerebral artery will reduce the force of the arterial jet. Logue (1956) has also had good results with this method; there is no doubt that proximal clipping of the appropriate

nterior cerebral artery has a big part to play in the early treatment of this group f ruptured aneurysms. Gillingham (1958) prefers to use a corrugated clip rather nan the ordinary Cushing clip, as he has had the experience of a firmly closed Cushing clip being progressively dislodged after a month with fatal haemorrhage rom the aneurysm. If there is not an adequate cross circulation, then clip occlusion f the aneurysm or its neck is the only adequate method of treatment.

In Gillingham's (1958) series, 21 of the 80 patients treated had anterior com-nunicating aneurysms; 12 patients were operated upon in the first 3 weeks and died; the remaining 4 are alive and well. Nine patients were operated upon after weeks; 6 are alive and well; 2 are dead and 1 is seriously disabled The two atients died because of further rupture of the aneurysm after they had left hospital. ome of his earlier cases were operated by direct attack on the aneurysm itself, ut since 1953 clip occlusion of the appropriate anterior cerebral artery has been referred with remarkable lowering of mortality and morbidity Operation carried ut 3 weeks or more after rupture resulted in greatly reduced mortality. In his xperience he is satisfied that this type of operation is the method of choice in nterior communicating aneurysms, provided there is an adequate cross circulation nd the patient is not in coma.

Botterell and his colleagues (1958), using general anaesthesia and hypothermia, ttacked directly 29 ruptured aneurysms of the anterior cerebral-anterior com-nunicating system; 20 of their patients were operated upon within the first 7 days fter rupture, there were 9 deaths. Nine patients were operated upon 7 days or nore after rupture with only 1 death. Of the 19 survivors, 16 were classified as aving excellent results, 3 having bad results These figures are possibly somewhat etter than Gillingham's in this type of aneurysm, but there is no evidence to uggest that this is because of the use of hypothermia, although Botterell and his olleagues believe that the deleterious effects of spasm may be avoided when ypothermia outlasts the spasm.

It would be optimistic to expect results in this group of aneurysms comparable o those achieved in the internal carotid and middle cerebral groups. Their natomical position is against this It seems likely that the trend will be to leave hese lesions as long as possible before operating, in order to assess what permanent lamage has been done at the time of initial bleeding There is no case for early operation unless consciousness is retained and accurate assessment of the mental tate can be made

ANEURYSMS OF THE ANTERIOR CEREBRAL ARTERY

Aneurysms on the peripheral distribution of the anterior cerebral artery are rare. Their approximate incidence may be judged from Gillingham's (1958) figures; of 80 ruptured aneurysms, 3 were found at the junction of the pericallosal and supramarginal branches of the anterior cerebral artery, at the genu of the corpus callosum This type of aneurysm tends to disrupt brain tissue with haematoma formation and if bleeding is posteriorly placed the clinical picture is similar to that of rupture of an anterior communicating aneurysm and with the same risk of grave nervous damage At other times bleeding occurs in a forward direction into the frontal lobe; if repeated minor leaks occur a blood cyst may form In

one such case the present author was able to excise an aneurysm 2·4×1·2 centimetres which had ruptured and formed two cysts in the frontal lobe, the more posteriorly placed cyst having a fine communication with the lateral ventricle (Whalley, 1949) Usually it is sufficient to clip or ligate the neck of the aneurysm. Provided there has not been serious intrinsic brain damage at the time of rupture the end results are excellent.

ANEURYSMS OF THE VERTEBRAL-BASILAR SYSTEM OF ARTERIES

While the incidence of ruptured aneurysm in this group of vessels is considerably less than that arising from the anterior part of the circle of Willis, it is probably true to say that if routine vertebral arteriography was performed when bilateral carotid arteriography has been negative, more aneurysms would be demonstrated. Gillingham (1958) adopted this routine Aneurysms of the basilar artery are extremely difficult to approach and treat. Aneurysms on the posterior inferior cerebellar artery which have ruptured, however, may be dealt with successfully. de Saussure, Hunter and Robertson (1958) have reported 2 examples of ruptured aneurysm of the posterior inferior cerebellar artery which they localized accurately by vertebral arteriography and successfully treated by clipping. Schwartz (1948) reported the successful treatment of a ruptured aneurysm arising from an abnormal vessel in the posterior fossa Rizzoli and Hayes (1953) also have reported a successful operation for a ruptured aneurysm arising from the left posterior inferior cerebellar artery. de Saussure, Hunter and Robertson state that the risk of clipping the posterior inferior cerebellar artery has to be weighed against the risk of further subarachnoid haemorrhage Their 2 patients did well ultimately. Their experience shows that the residual effects from clipping the artery are quite minimal and, they believe, are preferable to the risk of repeated haemorrhage. Provided the patient is reasonably co-operative after the initial haemorrhage, careful neurological examination may point to the posterior fossa as the likely site of bleeding.

HYPOTHERMIA IN OPERATION FOR RUPTURED ANEURYSM

Botterell and his colleagues (1958) believe that hypothermia with cervical arterial occlusion have improved the direct surgical treatment of ruptured aneurysm. [illegible]

[illegible]

volume which accompanies hypothermia results in a brain which is [illegible] to retract with consequent facilitation of exposure, particularly in deeply situated aneurysms in the supraoptic region. Their total mortality in 73 cases of ruptured aneurysm was 23·2 per cent This is approximately the same as Gillingham's (1958) figure—he had an overall mortality of 21·25 per cent in a series of 80 cases; here hypothermia was not used. These figures, of course, include all cases whether operated early or late. The percentage recovery becomes much greater the longer operation can be delayed, but during this waiting period the surgeon is all too aware of the danger of further haemorrhage.

CONCLUSION

In the present state of our knowledge it is extremely difficult to assess with any accuracy exactly how much better surgical treatment is than expectant treatment. Surgery in certain types of aneurysm produces better results when it is delayed. McKissock, Paine and Walsh (1958) studied 455 patients suffering from subarachnoid haemorrhage of whom 261 had intracranial aneurysms. After a very detailed analysis of untreated and operated cases they have come to the conclusion that there is no conclusive evidence indicating the natural death rate in a large series of unselected cases of ruptured intracranial aneurysms, so there can be no proof of the value of surgical treatment. They have been forced to the conclusion that the truth of this controversial matter can only be established by a pre-arranged campaign After consultation with neurologists they have put into operation a scheme whereby all patients suffering from ruptured intracranial aneurysm demonstrated by arteriography, and which, in the opinion of the surgeon, is amenable to surgical treatment, will be admitted to the trial series. Conservative or operative treatment will be allotted by random selection from previously prepared cards. They hope to get 350 patients in the trial series in order to gain a significant result which they expect to achieve in less than 2 years It will then be possible (they state), for the first time, to determine the natural death rate in this condition and the results of surgery in their hands

All surgical material is necessarily selected and rightly so The surgeon must be guided by his clinical judgment as in all other forms of surgery All things being equal it is logical that the correct way to deal with a ruptured aneurysm is to obliterate it directly if there is a reasonable chance of success There is no justification for attacking an aneurysm directly if, as a result of operative manipulation, patients are going to be left aphasic or demented In the light of our present knowledge the surgeon must have some preconceived idea of what it is right to do in any given situation, bearing in mind the tendency of these aneurysms to recurrent haemorrhage. The risks of operation have to be weighed against this possibility, the patient's relatives must be informed of the respective merits and demerits of surgery and expectant treatment. There is more to the treatment of a ruptured intracranial aneurysm than the knowledge of how to obliterate it. All facets of the problem must be studied and understood. Long-term results and the effect of these on the happiness of the individual and his relatives must be always in the forefront of the surgeon's mind It is the author's experience that if judgment is exercised along these lines, together with careful clinical assessment, operative treatment is well worth while in subarachnoid haemorrhage secondary to ruptured aneurysm From what has been written above, it will be seen that there is very little to suggest that this condition should be regarded as a surgical emergency, except in those instances where expansion of intracerebral clot is endangering the life of the patient.

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RESTRICTED ORBITAL CORTEX UNDERCUTTING IN THE TREATMENT OF PSYCHOSIS AND PSYCHONEUROSIS

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It is now accepted that surgical treatment confers benefit in a variety of psychiatric disorders. The results, however, are at times capricious, success in one case being followed by disconcerting failure in a comparable patient, or more rarely by physical or mental blemish disproportionate to the extent of the planned incision. These defects are inherent chiefly in blind operations in which at times the incision fails to reach the desired objective or its effects are extended beyond the appropriate plane by concealed haemorrhage. For these reasons, more time-consuming open operations which permit the position of an incision to be checked under direct vision, and which ensure complete haemostasis, may be preferable, particularly if it can be shown that a successful result depends upon accurate division of certain fibre tracts and not, as is sometimes assumed, merely the quantum of damage inflicted on the frontal lobes

DEVELOPMENT OF SURGICAL TREATMENT

The surgical treatment of mental illness may be regarded as the surgery of the thalamo-frontal and fronto-thalamic connexions which serve as the pathways of emotional appreciation and reaction, for the benefits obtained are in the emotional sphere and result from an alteration in the patient's emotional reaction, leading to greater emotional stability, the relief of distress, and improvement in intellectual activity due to a diminution of emotional distraction. At times secondary psychosomatic and autonomic changes accompany the relief of emotional tension.

Since Moniz (1936) injected alcohol into the frontal lobes in an attempt to cure delusions but obtained instead an improvement in emotional stability, a variety of procedures have been devised which seek to interrupt the connexions of the frontal cortex Early operations such as those of Lima (Moniz and Lima, 1936), Rizzatti and Borgarello (1938) and Lyerley (1938) sought merely to destroy a proportion of the central core of white matter without specific reference to any one group of fibres.

Standard operation of Freeman and Watts

Freeman and Watts' (1942) method of standard leucotomy is still used in many clinics today despite its drawbacks. This is a blind procedure in which a leucotome is introduced on both sides at a point 3 centimetres behind the outer margin of the eye and 5–6 centimetres above the zygoma and moved up and down in the plane of the coronal suture to divide the centrum ovale just in front of the anterior horns of the ventricle. It is not performed under direct vision and as Curran and Partridge (1952) remarked "Post mortem studies show that there is in fact a wide variation in the site and extent of the section, even in cases operated on by the same surgeon. The point of entry of the leucotome can vary by as much as 2 centimetres and the amount of white matter cut can be as little as 10 per cent of that which is intended These variations are due to the great differences in the topography of individual skulls and their contents, and there is also evidence that the instrument may push aside the fibres instead of dividing them, so that its excursion does not necessarily produce a comparable cut" These observations account satisfactorily for the uncertainty of the results obtained. An accurate incision divides the thalamo-frontal projection from the dorsomedial nucleus of the thalamus and it has been assumed that the emotional changes produced are related to the degeneration which occurs in that nucleus The incision is, however, wasteful in that it cuts across many antero-posteriorly directed fibres producing an extensive bilateral frontal lesion which is attended by blemish to the personality. There is also a high incidence of epilepsy and, even in successful cases, division of all fibres concerned in emotional appreciation produces an excessive emotional flattening and diminution of capacity for enjoyment, to which Strom-Olsen and Tow (1949) have drawn attention.

Strom-Olsen, Last and Brodie (1943), discussing the Runwell Hospital series, stated "Important changes take place in the connative affective sphere and not in the cognitive. In delusional, hallucinatory and tension states there appears to have arisen in those who responded well an indifference, even apathy, on the part of the patient towards his psychotic thought content, resulting in a calmer attitude and consequent abolition or lessening of psychomotor unrest and an improvement in behaviour. In the successfully treated depressive states the action is similar, easing of tension with consequent loss of agitation and depression—the thought content undergoes little change. In all the relevant cases except one, the delusions and hallucinations persisted though they often seemed less obtrusive and more shadowy than formerly". The best results were obtained in patients with severe disturbance of behaviour such as excitement, aggressiveness, violence, destructiveness and, in those showing tension and agitation, with consequent improvement in work output and ease of management, but whilst the operation was of benefit in severely disturbed psychotic patients it was considered that "In view of the risk of producing undesirable new symptoms, both mental and physical, the operation should only be undertaken when all other methods of treatment have failed, and where it can reasonably be assumed that the chances of remission or recovery are very remote. In other words one must strike the happy mean between relief of distressing symptoms and sacrifice of frontal lobe". Obviously,

such a damaging procedure could not be considered in the treatment of psychoneurotic patients in many of whom a comparable relief of tension and agitation would otherwise be desirable. It was necessary to devise a procedure which would relieve harmful emotions whilst leaving normal emotion and personality undisturbed.

Lower segment leucotomy

In 1942 in association with Dr Rolf Strom-Olsen a series of trial incisions were made differing in plane and extent. At an early stage we found that anterior incisions under the convexity produced insufficient therapeutic effect in psychotic patients whereas incisions placed too far posteriorly would cause serious autonomic disturbances and should never be employed We postulated (Knight, 1943) "That by still greater modification and reduction in the extent and situation of the cut—perhaps by confining the section to the lowest fibres of the lobe—it may be possible to remove obsessional symptoms without the least trace of reduction in the normal activities of the frontal lobe" We therefore employed lower segment leucotomy dividing the lower and inner fibres to ensure division of the thalamo-cortical relay whilst omitting all the upper portion of the Freeman cut This latter appeared to have been both wasteful and unnecessary, for the results showed a distinct improvement, eliminating much of the evidence of frontal lobe damage which had occasionally produced retardation, euphoria, irritability or childish behaviour in patients subjected to a full cut. Post-operative incontinence was hardly ever seen. There was likewise a diminution in the incidence of epilepsy. This operation was subsequently employed in the treatment of psychoneurotic individuals Elsewhere others developed a similar procedure and, further, more radical modifications of the original leucotomy were performed and Sargant (1953) drew attention to their value and recommended their use in intractable psychosomatic states, in anxiety hysteria, and in anxiety and depressive states with obsessional personalities.

Localized operations

Le Gros Clark and Boggon (1933) and Le Gros Clark (1948) had shown that a large part of the frontal cortex is an afferent projection area for the dorsomedial nucleus of the thalamus, comparable with the projection areas of the visual and auditory areas of the cortex. Fibres from the antero-posterior axis of the dorsomedial nucleus project in serial order on to the antero-posterior axis of the frontal lobe, to the cingulate convexity and orbital surfaces (Fig 58) Since the dorsomedial nucleus of the thalamus relays impulses originating in the hypothalamus, the [illegible]

[illegible]

of these connexions alone whilst leaving the remainder of the frontal cortex undisturbed

Localized operations were performed upon individual projection pathways by excision of limited cortical areas (cingulate, superior convexity and orbital), by topectomy (Penfield, 1948; Pool, 1949) and by undercutting similar areas

(Scoville, 1949; McKissock, 1951) leaving the cortex intact but severing afferent and efferent fibres passing to and from the selected zones in order to modify emotional behaviour whilst minimizing concomitant damage to personality and intellect. Preceding and motivating this change in surgical orientation there had been a change in conception of the nature of intellectual and emotional activity. It was realized that the function of the intelligence might be profoundly disturbed by stimuli ascending from the hippocampus and hypothalamus which are concerned with autonomic and emotional activity in the affective sphere.

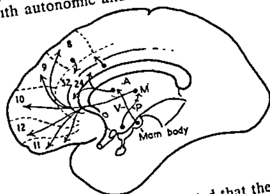


FIG 58 —Diagrammatic representation showing distribution of the thalamo-frontal radiation to the cortical areas of the frontal lobe

Papez (1937) had suggested that the hypothalamus, gyrus cinguli, hippocampus and their connexions were the probable anatomical substratum of the emotions. In elaborating this theory he displayed the wide connexions which exist between the hippocampus, hypothalamus and thalamus and between the thalamus, gyrus cinguli and frontal cortex. In his view somatic (including visceral) impulses which entered the circuits of these basal areas obtained emotional colour and finally reached the cortical level as "a stream of feeling" modifying the function of the cortical regions. This theory would suggest that the pathways connecting the thalamus to the orbital cortex and other regions of the frontal lobe contain the afferent projection systems for emotion. It is noteworthy that each of these areas gives rise to efferent fibres passing towards the hypothalamus which could constitute the pathways for emotional reaction. As Le Gros Clark (1952) has stated "It has come to be realized that intellectual and emotional processes are so intimately interlocked in any form of mental activity that it is not possible to separate them even as arbitrary categories Intellectual processes are only capable of normal expression if they are activated and directed by the driving power of emotional processes. The cerebral cortex may be structurally intact but its function can be grossly deranged if it is thrown out of gear with those more primitive parts of the brain which provide neural bases of emotional reaction".

In extending the surgical treatment of mental disorder to the sphere of the neurotic and psychoneurotic it is to the relief of an abnormal emotional charge disturbing the function of intelligence that the treatment appears to be most directly applied

Orbital undercutting

In 1950 we employed the operation of orbital undercutting devised by Scoville (1949). In 10 patients who had not benefited from leucotomy the operation gave

results which, in Dr. Strom-Olsen's opinion, justified its extension to patients with neurotic tension, in whom Scoville had claimed success.

Scoville (1949) had described the techniques for undercutting each of the three cortical areas—cingulate, superior convexity and orbital. That the orbital technique was most likely to lower neurotic tension without causing a serious intellectual deficit was suggested by the observations of Rylander (1939) which indicated that lesions of the orbital aspect of the frontal lobe produced changes in emotional tone rather than in intellectual or psychomotor activity. Rylander (1952) has shown by psychometric studies that lesions on the superolateral aspect of the frontal lobe are more likely to produce intellectual disturbances. Experimental evidence also shows that stimulation of the orbital areas produce autonomic responses, and ablation of those areas, tranquillity and loss of fear We were

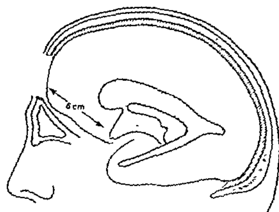


FIG. 59.—Diagrammatic representation of the plane of the incision and site of the trephine opening (Reproduced by courtesy of the Editor of *The Lancet*)

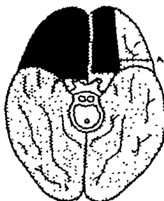


FIG 60—Diagrammatic representation showing, on the left, Scoville's operation and, on the right, the restricted orbital undercutting of a zone on the inner aspect of the orbital surface and at A the site of a lateral leucotomy incision

attracted to the orbital operation for these reasons and the fact that anatomically the line of the incision in the lower and anterior part of the lobe was so placed that it would not interrupt antero-posterior relays at a higher level and whilst severing the thalamo-orbital projection and thus possibly relieving harmful emotions, would leave sufficient pathways open elsewhere for normal emotional appreciation (Figs. 59 and 60).

Scoville aimed to undercut the entire orbital surface including the prechiasmatic area as far back as the anterior clinoid process and as far laterally as the junction of grey and white matter on the lateral aspect of the lobe. We omitted the lateral portion of this cut confining the incision to a narrow zone about 2 centimetres wide passing back on the inner aspect of the lobe just lateral to the mesial grey matter to a point beneath the anterior limb of the internal capsule at a depth of

5·5 centimetres from the frontal pole. This modification was introduced to produce further evidence of the importance of the ventromesial fibres and to avoid damage to the hippocampal relays in the lateral portions of the lobe. Our earliest successful cases had already had a full leucotomy performed from the side, and hence it appeared that not only did the vertical portion of a leucotomy incision play no part in contributing to the successful result, but also that the lateral or outer part of that incision in the orbital aspect might well be wasteful (*see* Fig. 60—A)

Myers (1947) concluded that the pars magnacellularis of the dorsomedial nucleus projects to the orbital frontal cortex. All the fibres passing to the orbital cortex spread thereto from the posteromedial aspect of the lobe and it is this area that has to be cut at the point of concentration of the fibres below the pars frontalis of the internal capsule rather than the outlying parts of the white matter towards the

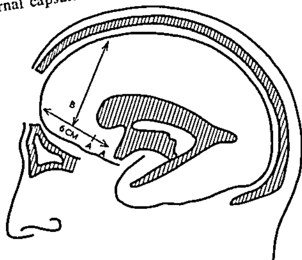


FIG 61 —Diagrammatic representation showing A–A, the posterior extension of the orbital incision at a second operation and, at B, the approximate site of the rostral scar.

inferior frontal convolution. Although it has been suggested that section of the uncinate fasciculus is more important in prefrontal leucotomy than division of the thalamo-cortical fibres, except where the objective is the relief of pain, we remained unconvinced on this point and have described elsewhere considerations which led us to avoid damage to the lateral portion of the lobe (Knight and Tredgold, 1955). The results obtained by this limited incision have been satisfactory and appear to indicate that there is an important area from which the good effect has been obtained (Fig 61). In 3 cases a first operation with a 5-centimetre cut failed, but a second operation which extended the cut posteriorly for a further centimetre produced success. We have operated so far upon 5 cases of failed rostral leucotomy. At operation the rostral scar was found at a point some 2·5 centimetres from the frontal pole, sometimes lying at a level above the plane of our operation which had been undisturbed by the rostral cut. A routine incision formed in the standard manner extending behind the plane of the rostral scar succeeded in relieving these patients. It therefore appears that the division of fibres passing from the anterior limb of the internal capsule to the orbital cortex plays an important part in producing improvement. Obviously these are not the only fibres which have to be

considered; if that were so, operations elsewhere could not succeed, but there would appear to be a concentration of fibres at this point which are possibly concerned in primitive reactions since they are distributed to areas of polar cortex from which autonomic reactions can be obtained. Division of these fibres alone can produce adequate relief of symptoms without the necessity of cutting across the substance of the lobe with a vertical incision or disturbing fibres elsewhere in the brain.

The operation of orbital undercutting takes time to perform but we believe that is justified. The incision can be checked by definite landmarks permitting accurate operation in elderly patients in whom cortical atrophy is present Complete haemostasis can be obtained in a manner that is impossible in blind operations, and it is noteworthy that in this series there has been a conspicuous absence of undesirable sequelae such as change of personality, irritability, intellectual or emotional flattening, increased appetite, adiposity or incontinence, which sometimes complicate blind procedures.

OPERATION

A transverse scalp incision is concealed within the hair line of the frontal region. In balding patients a butterfly curved incision can follow the edge of the remaining hair. The anterior scalp flap so formed is reflected forwards to expose the frontal bones as far down as the level of the orbital margins. A flap of pericranium corresponding to the exposed area is similarly reflected forwards after mobilization of the fascia from the line of the temporal crest on each side, thus exposing the frontal bones Bilateral trephine openings 3·75 centimetres in diameter are now fashioned above the level of the frontal sinus and extending to within 1 centimetre of the midline on each side. The bone discs, marked to indicate their position before removal, are preserved for subsequent replacement and bone dust is collected for later use. If the sinuses are abnormally high these trephine circles may be placed more laterally in order to ensure that the exposure is sufficiently close to the floor of the anterior fossa The exposed dura is incised transversely in the lower third of the exposed area and stay sutures are inserted A zone of the frontal cortex is now selected at a point 2 centimetres from the level of the floor of the anterior fossa and 1 centimetre from the falx as measured by a ventricular needle and an incision 2 5 centimetres wide is made transversely in the cortex at this point A cleft, 2 centimetres wide, is now opened in the white matter and deepened Spatula forceps marked in centimetres are inserted into the cortical incision and the white matter is gradually divided with a fine suction tube at the junction of the grey and white matter about 1 centimetre above the orbital plate on each side, the incision being kept parallel to the orbital roof as far back as a point 5·5–6 centimetres from the frontal pole. The incision is practically bloodless. Occasional bleeding points are seen on the inner aspect of the incision near the grey matter and are arrested by pressure or electrocoagulation It is not necessary to lift the frontal lobe from the floor of the anterior fossa to check the position of the cut; the distance of the incision from the orbital roof can be readily checked by puncture with a ventricular needle. An incision 2 centimetres wide gives adequate exposure in the depth if use is made of the reflexion of light from the

lower blade of the spatula; this will permit clear vision at a *depth of 5·5 centimetres*. At this point the terminal portion of the incision lies beneath the anterior limb of the internal capsule and here it is widened slightly to 2·5 centimetres in order to catch the fibres which are passing laterally from the capsule. Complete haemostasis is essential A roll of moist lintine the same size and shape as a cigarette can be placed in the cleft to exert pressure on small capillary points. When the incision is dry the dura is closed with silk sutures and the bone discs are replaced and moulded into position with bone wax. A small quantity of bone dust may be placed to conceal any rough edge and the pericranium is then sewn back into position concealing any minor surface irregularity. The wound is sutured in layers. With the incision concealed within the hair line the site of operation is not detectable.

POST-OPERATIVE CARE

The post-operative course is smoother than that following major leucotomy. There is no incontinence. There may be some drowsiness for 24 hours but most patients are fully orientated on the day following operation. Within 4 days they can be allowed out of bed, by which time relief of tension is often apparent. After standard leucotomy patients are in a flat and torpid condition, often incontinent for some while and thereafter have to be pushed into a stimulating regime to overcome post-operative lethargy. Following orbital undercutting the problems of rehabilitation are less, for patients are more active and interested and may resume activity within a few days (Fig. 62) A beneficial effect may be observed at once or a slow but steady progressive improvement may continue for as long as 18 months from the date of operation. Many neurotics and psychoneurotics after a short period of convalescence return to their home environment, if that is suitable, and there lead an active life, or return to occupation without the need for the constant drive and stimulation required to support a leucotomized patient. Every case must, however, be treated individually; what is suitable for one patient may be entirely wrong for another Return to home environment may constitute a harmful stress situation where the illness has arisen from emotional stress within that environment; in such cases, return to rehabilitation under psychiatric care may be necessary before final placement. Return to a mental hospital may itself be stressful in certain sensitive individuals and in those, hostel accommodation that gives opportunity for relaxation and entertainment may be beneficial before final placement in work. The greatest problems arise in the schizophrenic, psychopathic or hysterical individuals who may take a long time to establish sufficient strength of purpose to engage in occupation, requiring prolonged psychiatric support in a mental hospital followed by psychiatric supervision and encouragement on an out-patient basis. In all cases, wherever possible, drugs should be avoided during the period of rehabilitation. Barbiturates and tranquillizers may retard rather than accelerate recovery.

INDICATIONS

The failure of psychiatric treatment including electroconvulsive therapy is no contra-indication to operation. All our patients have been treated by psychiatric

measures including psychotherapy, insulin, electroconvulsive therapy and tranquillizing drugs without benefit before operation, sometimes for as long as 12–15 years in those who have later responded to operation within weeks or months. Previous operations have also been performed including the full Freeman cut and blind rostral operations—we do not regard these as necessarily precluding the possibility of success, as there seems to be evidence that blind procedures may at times fail to reach their objective.

Knight and Tredgold (1955), in their analysis, showed that patients who responded well to electroconvulsive therapy and those who did not respond, made equally



(*a*)



(*b*)

FIG 62 — [illegible]
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agitation. [illegible]
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There are [illegible]
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good recoveries after operation. Age bore little relationship to prognosis, equally good results being obtained in the age groups from 20 to 60 years or over. The duration of symptoms was likewise of little significance although patients with syndromes of less than 10 years' duration did slightly better than those whose symptoms were more long standing. With regard to previous personality, the only relative conclusion was that hysterical personalities, like hysterical symptoms, generally gave less ground for hope. Depression, lack of confidence, lack of

interest, anxiety, phobias, obsessions, "blackouts", severe insomnia and loss of weight, were the symptoms most favourably influenced, whereas impairment of memory and concentration were sometimes made better and sometimes worse. In general it appears that the operation produces tranquillity, and patients with syndromes which are characterized by great emotional tension or compulsion or by fear of any type, whether it be fear of self, fear of possible personal action, fear of imagined consequences of past actions, fear of the future, fear of environment or of distressing delusions or hallucinations, are likely to derive benefit. The operation will relieve these aspects of the total situation and when these have been removed the underlying personality of the individual becomes more clearly revealed so that the well preserved personality recovers well; the hysteric, the psychopath or schizophrenic, relieved of their distress remain, from their nature, continuing psychiatric problems. Therefore the operation succeeds best in agitated depression in which electroconvulsive therapy may produce unsatisfactory results, in severe anxiety neurosis and undifferentiated tension states which have resisted treatment.

Depression

The operation is extremely effective in endogenous depression and in reactive depression where that depression has its basis in personal suffering such as pain or tinnitus, it is somewhat less effective in reactive depression due to environmental causes if the patient has to return to that environment. Gratifying results may be achieved in depressive stupor. One patient, confined to an asylum for 7 years, who never spoke herself and who, if spoken to, would only reply "What is the use, I am dead", left hospital 3 months after operation and 3 months later organized Christmas for her family who regarded her recovery as being 100 per cent.

Hysterical syndromes

In hysterical syndromes operation can relieve anxiety and tension symptoms in an hysterical personality, but in selecting such cases care must be taken; everything depends on the amount of emotional tension present, on the degree of genuine fear and concern that the patient feels for his imagined ill health A female aged 62 years, with a lifelong history of emotional ritualistic behaviour and hysterical symptoms, complaining of pains and a variety of other hypochondriacal symptoms, full of self-pity and inclined to histrionic display, complained of inability to walk, "It is only my will-power that enables me to screw myself up to facing things. I have to pray for help to get out of bed". She was considered to be incapable of living outside a mental hospital, but 3 years after operation stated that she had no pain anywhere, that she had gained common-sense independence, was better on her own, did not want anyone with her for support, and found life full of interest. She loved going to the theatre and had got all her old interests back. "Before operation I wanted to do nothing, now I love doing all these things again."

Obsessional states

In obsessional states, if there is a strong motivation, operation will relieve

ritualistic behaviour, but the chronic hand washer is, by repute, difficult to relieve by any measure. In some there is a hint of stereotypy; the ritual has become part of life without associated compulsion and these patients will not respond Obsessional ruminative states respond well, particularly those with a marked phobic content. Obsessional thinking is easier to relieve than obsessional behaviour.

Drug addiction and alcoholism

Successes have been obtained in cases of drug addiction and alcoholism when the cause of the addiction has been an escape for a tension situation, the patient seeking to sedate himself by the action of these agents.

Schizophrenia

In schizophrenia previous experience has shown that there is a marked difference in response between patients of different categories; those who are withdrawn and solitary with shallow affect, who exhibit emotional flatness and apathy, as in schizophrenia simplex, and those who show gross disorder of thought and action with periods of stupor intervening as in catatonia, are likely to respond badly, and therefore we have not attempted the operation in such cases. Severely agitated or disturbed patients whose personality is otherwise well preserved respond well, and it is noteworthy that with the reduction in emotional tension and distraction, delusional patterns and even hallucinosis may fade One paraphrenic girl confined in a side ward, having recovered and now earning her own living, told quite rationally why she had been shouting and raving; she believed that she heard the doctors shouting at her through the roof and as her tension decreased these voices faded from her mind The benefit is produced not only by forcing a remission in the downward course of the illness, but by altering the patients total emotional reaction in the same way as tranquillizing drugs render them more trustworthy and reliable so that they can be given the benefit of "open door treatment" and obtain the stimulation that comes from work and relaxation outside the cramped environment of a mental hospital

A young patient from South Africa had been confined in Pietermaritzberg for many years and, before operation, was completely intractable and vividly hallucinated This patient spoke sense to her relatives within 2 days of operation and after a period of 3 months during which she progressively outgrew stages of selfishness, argumentativeness and self-assertion, like a small child growing up, derived great benefit when allowed to spend her time in shopping and travelling about town Five months after operation she flew back to South Africa unaccompanied, obtained a post as secretary in a Government office which she has held satisfactorily at a time when others are being discharged for redundancy

The selection of schizophrenic patients for operation demands very careful and detailed study. In every case the effect of electroconvulsive therapy or insulin treatment should first be tried If these have failed and the patient is deteriorating, and the personality is well preserved, operation should be seriously considered.

RESULTS

The first 200 cases have been analysed purely according to their clinical result

and pre-operative classification. Patients classified as recovered are those who are relieved of symptoms, whose relatives state that they are relieved, who are working and leading a normal life. Improvement is harder to define and in this group are included those who still have some symptoms despite improvement but in whom there is no need for further psychiatric treatment except in the case of certain schizophrenics who are improved but remain inside mental hospitals. If any *significant symptoms persist the case is regarded as failed, although in fact it might* be described as slightly improved (Tables I and II). There has been a notable absence of undesirable side-effects or personality change. Knight and Tredgold (1955), in assessing the first 50 cases, remarked that "No deterioration in personality was evident to themselves or to any referring psychiatrist except in one case".

TABLE I

210 CASES ANALYSED ACCORDING TO PRE-OPERATIVE STATUS AND POST-OPERATIVE RESULT

		Recovered	*Improved No psychiatric treatment Slight symptoms*	*Failed*	*Deteriorated*	*Mortality*	*Epilepsy*
C. Psychiatrically disabled, that is, out of hospital but in need of constant psychiatric help and treatment including drugs and electroconvulsive therapy	65	41	16	6	1	1. Hypertensive	3
B Socially disabled, that is, out of hospital but unable to work	50	33	10	6	—	1. Hypertensive	2
A Totally disabled, that is, in mental hospitals	95	55	27	13	—	—	3
Total	210	129	53	25	1	2	8

TABLE II

POST-OPERATIVE RESULTS ANALYSED IN RELATION TO PRE-OPERATIVE STATUS AND TYPE OF PSYCHIATRIC ILLNESS

	Pre-operative status—see Table I	*Schizophrenia*	*Agitated depression, anxiety neurosis and tension states*	*Depression*	*Obsessional*	*Totals*
Recovered	C B A	1 4 6	27 13 31	6 10 15	7 6 3	
Totals		11	71	31	16	129
Improved	C B A	1 2 12	4 4 8	4 1 5	7 3 2	
Totals		15	16	10	12	53
Failed	C B A	— 2 6	2 1 2	2 2 3	2 1 2	
Totals		8	5	7	5	25

The patients remain warm and normal emotionally and many letters testify to the normal emotional reaction of the recovered case. There is no reduction of inhibition so that unlike leucotomized patients they are not inconsiderate, greedy, selfish or tactless. Intellectual change is never marked Some patients are a little inclined to take things easily, which might be regarded as evidence of flattening Impairment of concentration or memory is detectable in less than 10 per cent of cases and is never such as to cause any anxiety to the patient. Psychological tests, when employed, usually reveal an improved score. Secondary changes include the relief of acne, rosacea, pruritus and menorrhagia. Complications are few. Infection of bone discs occurred in 4 patients operated on outside the environment of the Neurosurgical Centre. The incidence of epilepsy has been low and then has only produced occasional fits easily controlled by medical measures. The

CONCLUSIONS

The restricted orbital undercutting is a safe method which minimizes the risk of producing unexpected blemish as a result of concealed haemorrhage. Harmful effects have not been known to occur with the operation but occasionally complicate blind procedures as in the following case.

A patient, aged 37 years, a good-looking, active housewife suffering from an obsessional compulsive ruminative state with fears and agitation, in whom an orbital undercut had

The effect of orbital undercutting appears to be somewhat more potent than that of other forms of modified leucotomy. Curran and Partridge (1952) considered that the effects of the leucotomy "undoubtedly depend on its extent. The standard operation, in our experience, confers the greatest relief of symptoms but is liable to be attended by damage to the personality More restricted operations may leave the personality intact but are often inadequate in relieving symptoms". In considering the value of different types of operation they remarked "The standard operation is the one which exerts the maximal effect, although it may also be fraught with more undesirable consequences When the symptoms are of extreme severity, it is unlikely that any less extensive operation will produce an effectual result Its modifications, though preferable in maintaining intactness of the personality, confer, in our opinion, less freedom from symptoms They do not do as much harm, they do not do as much good" In contrasting the effect of open and blind rostral leucotomy they mentioned that although the open rostral operation has been associated with benefit, a disconcerting number of cases relapse and need a more extensive cut. McKissock (1951) writing of the effect of the blind rostral operation stated "That the effect of the blind incision would automatically

increase the amount of damage to the white matter as the result of the inevitable haemorrhage and oedema which would follow". We believe that there is evidence that the effect of operation depends upon the site of the lesion rather than its volume and that so far as can be seen at present, operation at this site can succeed in relieving certain of the more serious cases without the necessity of accepting the inevitable blemish which will result from the full standard operation To what extent this is true remains to be determined.

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ABSTRACTS RELATING TO INTRACRANIAL ANEURYSM

Intracranial aneurysm

BERMAN (1958) discusses the problem of the intracranial aneurysm. The symptoms depend upon various factors, of which the most important is whether or not rupture has occurred. The most frequent sign, especially if the aneurysm has not ruptured, is extra-ocular palsy usually associated with intense pain in the eye or in the frontal or temporal regions; the attacks of pain may be followed by ptosis of the upper eyelid. A large suddenly expanding aneurysm in the cavernous sinus may cause ipsilateral exophthalmos by obstruction of venous drainage from the orbit. Radiography may demonstrate curved linear shadows produced by deposits of calcium on the walls of the aneurysm, and [illegible] is now almost a [illegible]

Vertebral angiog[illegible]

generally thought that it is a more dangerous procedure and that very little could be done if a lesion were to be demonstrated. An aneurysm of the internal carotid artery is generally located within the cavernous sinus or immediately above it. Subclinoid aneurysms are better protected against rupture than those above the cavernous sinus. The method of indirect surgical treatment of subclinoid aneurysms consists of ligation of either the

the aneurysm. A ruptured aneurysm is the most frequent cause of subarachnoid haemorrhage. Frequently, within a few days of a very mild episode of bleeding, signs

graphy demonstrated an adequate cross-circulation.

Intracranial arteriovenous aneurysms

Intracranial arteriovenous aneurysms are discussed by HOOK and JOHANSON (1958). A study has been made of 12 patients, of whom 9 were men and 3 were women. their

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was carried out with particular attention to the growth of the aneurysms, periods of observation ranged from 3½ to 21 years. In one of the cases in the series there were 2 aneurysms. The results of the study showed that 8 of the total of 13 aneurysms increased in size and the other 5 remained unchanged The increase in size was most marked in the aneurysms which were located in and around the Sylvian fissures and, in one instance, of suprasellar aneurysm Thrombosis had occurred in one of the aneurysms. The authors emphasize that in determining whether an increase or decrease has actually taken place in the calibre of the vessels, it is essential to consider whether there is vasospasm of the arteries Spasm does not appear to occur in the veins of the brain; the authors do not know of any case in which such phenomena have been described; vasospasm was not observed in any case in the present series. Cases of spontaneous thrombosis in these

considerably after total extirpation. Partial removal may have to be considered in some cases, for anatomical reasons, but would probably present greater technical difficulties, especially as regards haemostasis.

Effect on the cardiovascular system

The effect of intracranial arteriovenous aneurysms on the cardiovascular system has been investigated by HÖOK, WERKÖ and ÖHRBERG (1958). A study has been made of 14 patients, of whom 9 were men and 5 were women Their ages ranged from 16 to 63 years, the mean duration of clinical symptoms was 16 years, the size of the aneurysms ranged

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important symptoms referable to the cardiovascular system except in 2 cases. In one of these there was dyspnoea following exertion, and the patient already had auricular fibrillation at rest; in the other, there were mild symptoms of angina pectoris type, following exertion, without, however, any signs of coronary insufficiency during work tests. The data obtained from the histories of the 123 cases of arteriovenous aneurysm and of the 10 cases of carotid artery-cavernous sinus fistula, included hypertension in 5 cases, pathological electrocardiographic changes in 3 cases without other accompanying symptoms; subjective heart symptoms

be attributed to the arteriovenous aneurysm. The authors emphasize the necessity for careful evaluation if this is based on case histories alone.

Cerebral arteriovenous aneurysms

Surgical management

PARKINSON (1958) describes his clinical, angiographic and operative experience in 12 cases of cerebral arteriovenous aneurysm operated upon by direct intracranial approach between 1953 and 1956 He emphasizes that the local physical signs, enlargement, increased warmth

supply, the shunt and the draining veins were visualized separately. The terminal artery or arteries entering the shunt were found to be unbranched segments which did not supply anything else. He termed them "final feeding arteries". The draining veins pursue a very tortuous course and although usually only one or two, their tremendous looping may simulate the appearance of many more. The author considers that for successful surgical treatment the exact relationship of the "final feeding arteries" to adjacent normal trunks must be defined by angiography. The draining veins usually lie on the surface. Operation commences by teasing open the arachnoid where the large draining vein comes from the depth of the brain. The shunt is then visualized in a sulcus and the final feeding arteries clipped and severed. The entire shunt becomes relatively slack and this permits of the tying of the draining vein and removal of the shunt. Parkinson considered that deep x-ray therapy has no place in the treatment in view of the size of the vessels involved. Ligation of the ipsilateral carotid artery only results in reducing the pressure and volume of blood reaching the hemisphere. As the shunt will continue to siphon off the majority of blood, the hemisphere will be further deprived without lessening the risk of recurrent haemorrhages.

Cerebral arteriovenous anomalies

Intracranial haemorrhage

Intracranial haemorrhage in cerebral arteriovenous anomalies is discussed by WOOD and SVIEN (1958). A review has been made of the records of 51 patients in whom such

[illegible] ...ical attention and lasting less than 1 day.

only 3 instances occurred in patients less than 20 years of age; the subarachnoid

profound. The authors conclude that care must be used in considering subarachnoid

and Rolandic fissures.

Spontaneous intracranial haemorrhage

Surgical treatment

FALCONER (1958) quotes papers by many surgeons, who during the last decade have

to 6 per cent. One-hundred-and-nine patients with 118 aneurysms received operative treatment. Of those operated upon during the first week following bleeding 30 per cent died, while of those operated upon after the first week the overall mortality was 11 per

artery is likely. The patient should first be admitted to the nearest general hospital and if he survives the first week he should then be transferred to a hospital with neurosurgical

choice of operation which depends on the site and nature of the lesion. He concludes with a table showing that of 50 consecutive aneurysm patients, operation results were good in 38, poor in 5, with 3 operative and 4 late deaths.

Subarachnoid haemorrhage

Management

haemorrhage into 4 basic conditions, intracranial aneurysm, angiomatous malformation,

expanding, evacuation of the clot is relatively simple and often life-saving. They consider

the patient began to improve clinically. If operation is postponed, recurrent haemorrhage may occur at any time. The authors stressed the great importance of experience and judgment in assessing the case and selecting the appropriate treatment. They postulate that with advancing techniques such as hypotension and hypothermia the prognosis will soon be even better for those patients who are treated surgically shortly after bleeding has occurred.

Results of treatment

SIROIS and his colleagues (1958) reviewed the results of their treatment of 108 cases of subarachnoid haemorrhage. Of these 71 (65·7 per cent) were cured, 24 (22·3 per cent)

application of a Silverstone clip on the common carotid artery on the affected side which was pro
grams
weeks
if there
aneurysms.

Basilar artery insufficiency

Radiographic diagnosis and surgical treatment

CRAWFORD, DE BA
surgical treatment of
55-year old man who,
paralysis of the right side and partial paralysis of the left side of his body. These symptoms quickly became less severe and he was able to take his boat back to camp. Subsequent angiograms showed complete occlusion of the right and partial occlusion of the left vertebral arteries. At operation, hypertrophied intima containing atheromatous material was removed from the lumen of the left vertebral artery close to its origin from the

innominate, subclavian and left common carotid arteries
circulation was restored and the various neurological symptoms present before operation relieved.

ABSTRACTS RELATING TO NEUROSURGERY

Intractable pain

Leucotomy

ELITHORN, GLITHERO and SLATER (1958) report on the effect of leucotomy upon intractable pain affecting 13 men and 12 women aged 31–78 years. Patients were observed

social rating, but only 8 patients and 8 relatives considered that the operation had been of value. Only 5 patients were of the opinion that their pain was less intense. No fatalities resulted from the operation. Complications included delayed haemorrhage (1 case), epilepsy (3 cases) and excessive personality changes (2 cases). Relatively extensive opera-

the pain is not severe and the psychological reaction is a depressive or an anxious preoccupation with symptoms. Little permanent relief is to be expected, however, if the pain is severe and of frequent occurrence. Although hysterical symptoms may be increased after the operation, the total effect is often a gain in social adaptation. In selected cases, when pain cannot be alleviated by other means, a leucotomy-type operation may produce relief from suffering and an improvement in social adjustment.

Intrathecal phenol

NATHAN and SCOTT (1958) describe the treatment of intractable pain by means of intrathecal injections of phenol. In 30 cases the investigators employed phenol dissolved in glycerin and ethyl iodophenylundecylate (Myodil) to form a solution of 7·5 per cent. The dosage was 0 75–1·5 millilitre and in most cases the solution was injected caudal to the twelfth thoracic vertebra. No weakness of the musculature ensued, apart from the development of retention of urine and disorder of defaecation in one instance. Soon after administration of the solution the phenol content of the cerebrospinal fluid was relatively high near the site of the injection, but after the first hour the content was found to be considerably reduced. It was possible to move the patient within 15 minutes of the injec-

Six patients showed a slight increase in weakness of the musculature and there were 3 cases of disordered micturition or defaecation Nathan and Scott conclude that it is justifiable to inject the phenol solution for the relief of pain, especially when the pain is due to cancer On the other hand, the solution of silver nitrate is less safe.

Parkinsonism and disorders of involuntary movement

Chemopallidectomy and chemothamectomy

COOPER and BRAVO (1958) describe the use of chemopallidectomy in the management of tremor and rig

children Prior to

landmarks are ide

ventricle 6·5 centimetres beneath the cortex. Hypaque is injected into the cannula so that the solution inflates a balloon at the end of the instrument. A physiological lesion is thereby produced in the globus. The cannula is allowed to remain in the brain tissue and instillations of either alcohol or Etopalin are administered 24–48 hours after the operation. More effective results may be achieved by repeating the technique with the cannula placed in the region of the ventro-lateral nucleus of the thalamus. *Cooper and Bravo* have performed chemopallidectomy in more than 650 cases of parkinsonism. The treatment has relieved rigidity in 80 per cent of cases and tremor in approximately 75 per cent of cases. The mortality rate was 2·4 per cent and the incidence of hemiparesis was 2 per cent. No fatalities were recorded among a more recent series of 150 cases.

Tumours of the thalamus

cisternostomy was the operation of choice for patients with symptoms of intracranial hypertension, provided that the lateral ventricles were enlarged and the foramen of Monro

operation, without radiotherapy, was employed in 4 cases. As a result, one patient was alive and working 6 years later. When the operation was combined with a course of of 7 patients were alive and working 4½ and 8 years later, respectively.

3 months. The about 20 years

and complains of symptoms indicative of increased intracranial pressure for a period of less than 4 months before seeking advice. Hemiparesis, sensory loss and hemianopia may be present. Abnormal pupillary reactions and loss of conjugate deviation provide confirmation that the neoplasm is situated in the thalamus, perhaps in the mid-brain.

Cerebral tumours

Hypothermia in surgical treatment

SEDZIMIR and DUNDEE (1958) describe the use of hypothermia in the treatment of cerebral tumours. Pre-operative medication is with chlorpromazine. General anaesthesia is induced with thiopental, the larynx is sprayed with lidocaine and oral intubation is ... is maintained with

...minutes in order to aid
...ack, and ice-bags are
...temperature required,
...applied if the tempera-
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...cerebral oedema was
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of the tumours required relatively less manipulation and traction. No fatalities were recorded in the series, but the authors refer to a death due to mismanagement of a case of aneurysm. During the post-operative period the patient was cooled to 26°C and heart block supervened.

Thrombosis of internal carotid artery

CLARKE and HARRIS (1958) describe 5 cases in which thrombosis of the internal carotid artery gave rise to signs and symptoms resembling those produced by an intracranial space-occupying lesion One case-report concerned a man, aged 58 years, with a history of poor memory, short attacks of unconsciousness, severe intermittent left frontal headaches and weakness and numbness of the right hand and forearm On admission to hospital the patient was found to be lethargic Examination revealed right spastic hemiparesis, right homonymous hemianopia and bilateral papilloedema. A left carotid angiogram showed complete occlusion of the internal carotid artery The patient died 22 hours after angiography. Necropsy revealed thrombosis of the left internal carotid artery and massive infarction of the left cerebral hemisphere. Discussing the syndrome, the authors refer to the first manifestations, which include persistent headache, convulsions and unilateral progressive weakness and paraesthesiae of the limbs. Dysphasia occurs if the dominant hemisphere is affected Transient attacks of cerebral ischaemia produce episodes of disordered speech and paralysis of the limbs. Eventually the signs become permanent. During the second clinical phase drowsiness, papilloedema and all the signs of a cerebral tumour may appear. The findings often resemble those of malignant glioma Carotid angiography is of assistance in the differential diagnosis, but the test is not free from risk Direct inspection of the vessel may be required. The fatality rate for thrombosis of the internal carotid artery is 34 per cent, and a severe neurological deficit is likely to ensue in more than 50 per cent of cases. Apparently operation on the artery affords the only hope of a favourable outcome, but treatment is likely to be less effective when complete arterial occlusion has led to irreversible cerebral destruction

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PROGRESS IN CORNEAL GRAFT SURGERY

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"The old never dies till this happen, till all the soul of the good that was in it get itself transformed into the practical new".

Carlyle (1795-1881)

The progress of corneal graft surgery in recent years has been based on the establishment of principles of selection and technique which are now accepted throughout the world; in turn, this agreement has led to a sharp increase in the practice and scope of the operation. Then again, the emphasis of research has shifted from the operation theatre to the laboratory. For example, there have been few radical changes recently in the technique of keratoplasty, whereas there has been mounting interest in the biological behaviour of the corneal grafts and in methods of long-term graft preservation. It has become obvious that if the corneal graft is to play a full part in the treatment of blindness, on the international scale, there must always be an adequate supply of suitable donor material readily available throughout the world.

Major factors which determine the outcome of a corneal graft operation are the control of infection, the details of surgical technique, the correct assessment and selection of the case and the state of the donor graft; these are now examined.

CONTROL OF INFECTION

Few cases of infected grafts have been reported recently, whereas it will be remembered that infection was the commonest cause of failure in the last century. In over 400 grafts at the Queen Victoria Hospital, East Grinstead, there have been only 3 cases of severe infection. Two examples occurred in elderly men who had lost one eye years previously and who, therefore, had infected sockets. Both sockets contained *Escherichia coli* which escaped the pre-operative antibiotic screen and which later infected the grafts. When the organism was recognized, antibiotic control saved the eyes though both grafts became opaque and had to be replaced. Romanes (1958) reported the third case from the Unit and, because of the rarity of the organism, a few details may be of interest.

A young man had a perforating graft on his right eye for the treatment of conical cornea. A week after operation the graft was found to be grossly infected with *Micrococcus*

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No eyes have been lost from infection, and it is no exaggeration to say that today infection is no longer a menace, but a weak link in the chain of asepsis still remains and this rests with the condition of the donor graft. Nowadays, since there is an increasing number of eyes available for keratoplasty, fresh material is used as quickly as possible after removal from the cadaver, for it is well known that



FIG. 63—In this eye there was gross infection with *Micrococcus tetragenus* and perforation took place at the lower edge of the graft. The condition is seen 32 weeks after operation with corrected vision of 6/9; fortunately the scar and iris adhesion at the lower part of the graft do not seriously interfere with vision as the rest of the graft is perfectly clear. (*By courtesy of the Editor of the British Journal of Ophthalmology*)

the best grafts are obtained with the freshest material Undetected infection, however, may sometimes creep into the host eye by the very speed of this procedure and special care, therefore, to control contamination is necessary.

TECHNIQUE

Up to 1955 there was a steady spate of papers from all parts of the world which dealt with various methods of modification of technique for the successful prosecution of a corneal graft operation. This spate has now slackened because the basic principles of selection, fixation, graft section and post-operative care have been generally established and accepted Reports on corneal grafting in ophthalmic literature at the present time tend to be concerned mainly with the results.

There are, however, several important points of technique in the performance of the operation, examples of which are as follows. (*a*) The section of the host cornea should be exactly at right angles to the axis of the cornea, and it should be cleanly cut without any tags or sloping sides (*b*) Whatever method of fixation is used it should be adequate, overlay sutures with a plastic splint have been found satisfactory at East Grinstead for routine use (*c*) The field of operation should have been made sterile by previous antibiotic medication. (*d*) The pupils should be in full miosis so that the lens is completely protected from damage by the trephine (*e*) The donor graft should be cut at right angles to the donor cornea and should also have a perfect edge. It should be carefully inspected before it is put

into place and, as a rule, it should be 0·1 millimetre larger than the bed. Subconjunctival injections of cortisone are no longer recommended, and retrobulbar injections of local anaesthetic have been abandoned as they are liable to disturb the intra-ocular pressure.

Fixation of the graft

A first principle of success for a graft in any part of the body is that it shall be firmly held in position and that the junction between the host and donor shall be good. To obtain these objectives with corneal grafts there are three methods of fixation in general use today: (1) by overlay sutures; (2) by splint coverage; and (3) by interrupted multiple direct sutures

Overlay sutures

The use of overlay sutures represents one of the oldest methods of fixation still in use. Whilst this fixation is adequate for grafts up to 6 millimetres in diameter, it is unsafe for larger grafts towards which modern fashion veers. Sometimes the overlay sutures mark the graft when crossing it, and a graft may slip out between the limbs of the sutures if one leg happens to cut out Such a suture, however, is easy to insert by using a 7–10 millimetre Vogt/Barraquer or Jamieson Evans corneal needle armed with fine silk.

Corneal splints

Corneal splints have received renewed attention with the advances in the technique of the manufacture of plastic materials (Ainslie, 1956); this also applies to cataract surgery where the insertion of a plastic lens into the eye has come into common use. Now that a transparent thin wafer of plastic material, curved to the contour of the normal cornea, is available, ideal coverage for the graft becomes possible. At one time sterile egg membrane was used for this purpose but this has now been entirely out-moded by the plastic splint. The advantages of the plastic corneal splint are that it offers a firm contact to the graft which can be seen through it, and it may be used either with overlay stitches or with direct sutures through the splint itself. Very little irritation to the eye is caused by the presence of this splint (Fig. 64)

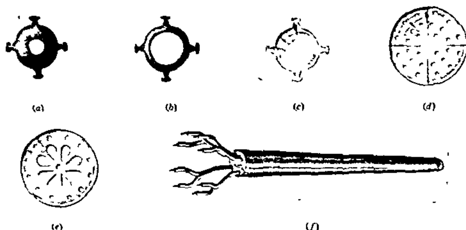
Sterilization of these splints is important, and at first Cetavlon was used. Unfortunately, this medium was toxic to the cells of the graft and the corneal splints are now mostly sterilized by the caustic soda method of Ridley (1957).

Direct suture

Direct suture of a corneal graft may be employed for all sizes of graft and this is a method which has been notably advanced by the Barraquer school in Barcelona. In Great Britain some surgeons use this method for all grafts, irrespective of size, whilst others reserve direct sutures for grafts of over 6 millimetres in diameter. The advantage of multiple sutures at right angles to the graft-host union is security, but there are also problems. For instance, sometimes a stitch cannot be firmly anchored in the host just where it is required, and the resultant suture has then to cross the line of section obliquely When this is tightened there is a tendency for distortion of the suture line to be produced. Also, stitches occasionally cut out and leave a weak gap in the line. At the end of a fortnight it has been found

that the fine silk used for these tiny sutures is difficult to remove because it has become covered by epithelium.

With the necessity for multiple needle punctures there is also an increased risk of entering the anterior chamber, and after such an accident corneal fistulae are frequently seen. Because of these many difficulties, Barraquer has now changed to the use of a continuous suture for fixation of penetration grafts; he uses a Grieshaber Vogt-Barraquer needle of 4–5 millimetres which is loaded with monofilament virgin silk



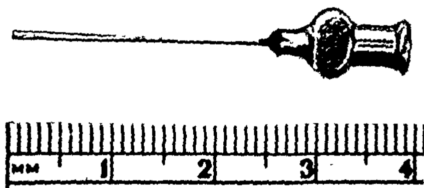
[illegible] differs from the original only in having considerably larger drainage holes. (f) Ainslie's corneal marker is for marking precisely on the cornea the locations for the retaining sutures Its eight short needle points exactly correspond with the suture holes of the splint (*By courtesy of Hamblin Ltd*)

Use of air for eyeball reconstitution

The use of air for the reconstitution of the eyeball after it has been opened is now commonplace in corneal graft and cataract surgery. After the corneal graft has been secured in place, a fine-angled air cannula is inserted between the graft and the host with as little disturbance as possible (Fig. 65) Air can then be blown into the anterior chamber, giving the dual advantage of opening the angle of the anterior chamber and forming a holding cushion on which the graft rests. The air is absorbed at the end of a week.

Instruments

The general pattern of instruments which are used in corneal graft surgery has changed very little in the past few years Trephines remain the most popular instruments for cutting the graft and the graft bed, though some surgeons, for example, Sjogren, prefer a punch (Fig. 66)





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Editor of the British Journal of Ophthalmology.)

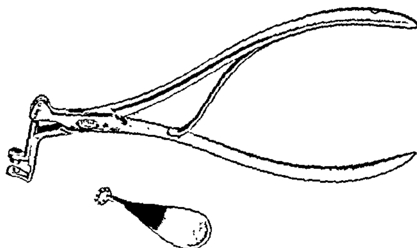


FIG. 66.—Sjögren's punch. The object of this punch is to enable clean-cut edges of donor and bed to be obtained. (*By courtesy of the Editor of the Transactions of the Ophthalmological Society of the United Kingdom.*)

In general, ophthalmic surgeons in Great Britain use the Franceschetti trephine

after allowing for the thickness of the body of the trephine An innovation of recent introduction for the section of split corneal grafts is the miniature electro-dermatome described by Castroviejo at the International Congress of Ophthalmology, 1958. In this instrument an electric motor drives a razor blade which can be adjusted to cut corneal grafts varying in thickness from 0·1 to 1·5 millimetres; it is claimed that grafts cut by this instrument are more even and regular than those cut by hand (Fig 67 *a* and *b*)

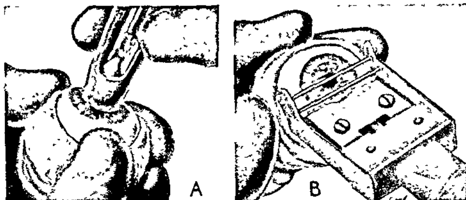


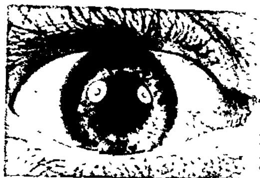
FIG 67 —(*a*) Trephine set to cut 0·1 millimetre deeper than the thickness of the lamellar graft, outlining the graft in the eye of the donor, (*b*) electro-keratotome dissecting the lamellar graft The thickness of these grafts can be adjusted by varying the cut of the blade The blade is driven by an electric motor and regularity of thickness is a feature of the graft (*By courtesy of the Editor of the American Journal of Ophthalmology*)

SELECTION OF CASES

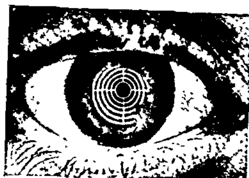
An expansion in the practice of the operation throughout the world now enables surgeons to predict more accurately those cases which are likely to succeed after a corneal graft operation Corneal grafts are performed either for the restoration of vision (optical graft) or to improve active disease of the eyeball (therapeutic graft)

Optical grafts

For an optical graft to succeed it is recognized that the host cornea should be free from active vascularization, and that in the host cornea there should be a proportion of normal corneal tissue against which the new graft can be placed. Also, as far as possible, the thickness of the host and donor corneas should be equal, though this is not always possible to obtain For these reasons corneal grafts which are carried out for conical cornea constitute the most successful group (Fig 68 *a*–*d*)



(*a*)



(*b*)



(*c*)



(*d*)

FIG 68.—(*a*) The result of a 7-millimetre full-thickness corneal graft on a case of severe keratoconus. The graft is *perfectly clear with regular edges and the light reflexes show* no distortion. The vision of this eye was improved from "counts fingers" to 6/6 without [illegible] of the surface [illegible] ner eye of the [illegible] he distortion [illegible] eration. (B[illegible]

Where, however, there is an excess of scar tissue, as in severe chemical burns, grafts are not so successful and it is necessary to adopt other techniques which prevent vascularization and reversion of the graft to scar tissue. For these difficult cases Leigh (1955) has recommended a special technique to prevent vascularization of the final optical graft (Fig. 69 *a–d*).

First, a 6-millimetre lamellar graft is prepared in the dense scar. When this is soundly healed, an annular lamellar graft is placed around it so as to block the entry of vessels coming from the limbus of the cornea into the graft area Finally, a full-thickness penetration graft is done through the previous lamellar graft, which should be clear of blood vessels. In this way it has been found possible to obtain transparent grafts in corneas which are completely opaque with dense fibrous tissue.

Therapeutic grafts

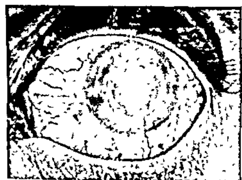
Therapeutic corneal grafts are usually of the split corneal or lamellar type, and are being used much more frequently for application to active corneal disease



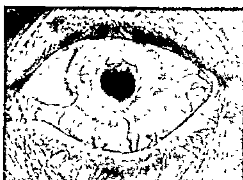
(a)



(b)



(c)



(d)



(a)



(b)

FIG 70 —(a) A severe central descemetocele in a case of Turner's syndrome (b) The descemetocele has been completely excised and replaced by a corneal graft which subsequently gave complete clarity and vision 6/9. (*By courtesy of the Queen Victoria Hospital, East Grinstead, Sussex*)

(Casey, 1958) Not only are they useful when applied to an indolent corneal ulcer which is slow to heal, but they have been found to be probably the most effective treatment for Mooren's ulcer of the cornea, a condition which has hitherto proved incurable.

Occasionally, a full-thickness therapeutic graft is used to replace a descemetocele and to restore the continuity of the eyeball (Fig. 70 *a* and *b*)

Grafting in aphakic eyes

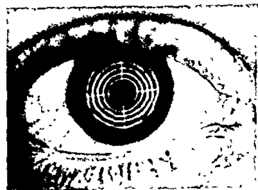
Hitherto the performance of a corneal graft in an eye from which the lens has been removed has always been considered a great hazard, but new techniques are bringing even these cases to success (Fig. 71 *a*, *b* and *c*). Professor Flieringa of Rotterdam has advised the use of rings which are stitched to the eyeball before the globe is opened in such an operation. This ring acts as a sack holder and



(*a*)



(*b*)



(*c*)

Fig 71.—(*a*) An aphakic eye with gross corneal scars before operation. [illegible] of light". (*b*) After [illegible]

prevents the collapse of the globe before the graft is in place. When the graft is secure air is blown in and the volume of the eyeball restored; the ring can then be removed.

Choice of graft

In early years, because of the risk of constant infection in consequence of opening the globe, the lamellar graft was widely used, but now that the operation is more safe the penetration graft is generally preferred. This type of graft has practically

entirely replaced the lamellar graft for optical purposes, and the lamellar graft tends to be reserved for preparatory or therapeutic grafts For the same reason that the operation is more safe the mushroom type of graft, introduced by Franceschetti, is hardly ever used and so it has come about that the full-thickness penetration corneal graft is almost exclusively used for optical purposes and the lamellar split corneal graft is retained for therapy.

CAUSES OF FAILURE

At this stage it is convenient to summarize the causes of failure in a corneal graft.

Inadequate technique

Inadequate technique is usually due to the absence of frequent opportunities for practice of the operation For this reason it is felt by some surgeons that corneal graft operations are best done in centres where greater practice can be obtained, and where there is a ready supply of donor material

Imperfect instruments

There is a wealth of exquisite instruments for corneal graft operations available to ophthalmic surgeons today. Great importance is placed on the perfection of the cutting edges of needles and trephines; these must always be inspected on the day before operation by the use of the slit lamp microscope.

Nursing difficulties

Corneal graft cases require special nursing, many of these patients are also totally deaf When such a patient has both eyes covered in addition to the deafness, he is completely cut off from the outside world and nurses have to be familiar with the special ways in which these patients have to be handled to make contact Special eye drops for each patient are essential and there must also be a lively awareness of general complications, such as chest trouble and thrombosis

The donor supply

If corneal grafts have to be done at isolated intervals in a general eye hospital, there is always the risk that a case will be admitted hurriedly to fit in with irregular donor supply This is an additional reason why it is better that these cases should be treated in special centres where there can be an orderly admission, and where there is an adequate supply of fresh and preserved donor material readily available. Moreover, the concentration of these cases tends to improve research

The host-donor corneal relationships

The condition of the host cornea before operation is carefully studied on the slit lamp, the absence or presence of active vascularization is noted, the area and density of the scar is assessed and, where possible, the corneal thickness is recorded (Fig 72). In the host eye there must be an absence of glaucoma and there must be accurate central and peripheral retinal function Where possible, lens changes

must be detected and noted. The standard of vision which justifies a corneal graft must be assessed for individual cases but, as a rule, binocular vision must not be better than 6/36 and it must not be possible to correct it beyond 6/12 with a contact glass. The patient must be unable to read newspaper print.

Preferably the donor material must be as fresh as possible and must certainly have been removed within 10 hours of death. It should come from a healthy eye which has not previously suffered from any corneal inflammation. If fresh material is not immediately obtainable, then the next choice is material preserved in water

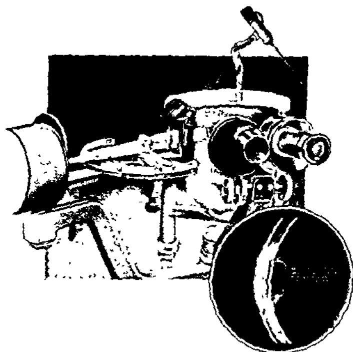


FIG. 72.—The *Corneal Pach*[illegible] transparency of the cornea it is possible by this instrument [illegible] iced by scar tissue. The estimatic[illegible] ight reflexes on the anterior an[illegible] rcks

vapour or oil at +4° C. Low temperature preservation at −79° C. is so far only suitable for lamellar grafts, although research into the use of this method for penetration grafts continues.

General condition of the patient

The general condition of the patient is also most important. It must be borne in mind that a case of full-thickness keratoplasty may have to remain in bed for up to 3 weeks, and this can be a considerable hazard in elderly people. Apart from lowered resistance to infection, such complications as hypostatic penumonia or myocardiac failure and thrombosis have all been recorded. Urinary obstruction is particularly prone to occur in these cases in the first 24 hours after operation.

Complications

Infection and displacement

Immediate complications after operation are infection and displacement of the graft, but these are, fortunately, now very rare. Later, iris adhesion to the graft may cause secondary glaucoma and, if the adhesion is considerable, it is better to remove it 2–3 weeks after the performance of keratoplasty than to allow glaucoma to develop. On the other hand, if the iris adhesion is only small and not causing trouble, removal may be delayed until later.

Persistent oedema

Persistent oedema of the graft without vascularization is a serious complication as it ruins the optical value of the graft (Fig 73). This condition may result from poor vitality of donor material, from unequal thickness of the host and donor cornea,



FIG 73.—Malady of the graft (*By courtesy of the Editor of the British Journal of Ophthalmology*)

allowing aqueous to enter the graft, and from poor adaptation of host and graft cornea. Under these conditions Descemet's membrane curls up and the graft becomes waterlogged from the entry of aqueous humour

Vascularization

Vascularization may be due to transient irritative effects, but when it persists it is considered to be due to an antigen reaction between the donor cornea and the host tissue Early steroid therapy has been found to be of some value in controlling neovascularization, beta radiation has not been generally successful and has definite disadvantages

THE DONOR GRAFT

Thanks to factual publicity on television, radio and in the national press, the objects which were envisaged by the Corneal Grafting Act, 1952 (*see* Appendix on page 318), have been largely achieved By these means the public conscience has been stirred and legal bequests of eyes for corneal graft operations have steadily increased in numbers. For example, at the Corneo-Plastic Unit at East Grinstead in 1951 the number of available eyes was 37, but in 1956, after the Act had become law, it rose to 212 eyes

The system of collection at this Regional Eye Bank is simple Generally, the medical practitioner notifies the Unit immediately death has taken place, he is

aware that the bequest of eyes has been made and that the relatives are in agreement. A duty registrar leaves at once with equipment adequate for the sterile removal of the eyes, and he takes care to ensure that there is no disfigurement. After the eyes have been removed they are placed in sterile wide-mouthed glass vials containing an antibiotic medium, and they are brought back to the Unit in a box, surrounded by ice. At the Eye Bank they are then placed either in the refrigerator at +4° C., or in the low temperature bank at −79° C., where the temperature is maintained by carbon dioxide snow. At present the collection of bequest eyes involves about three visits per fortnight, and the value of fresh material thus obtained is immense.

The storage of donor eyes

There is no doubt that throughout the world there is a shortage of readily available corneal grafts. This is made more acute by the increasing number of ophthalmic surgeons who now wish to perform the operation, and also by the widening scope of conditions for which the operation itself may be used. Thus, to prevent the waste of donor eyes and to have a source of graft material always available, some method of preservation or banking is essential

Short-term preservation

At present there are two practical methods of preservation in general use but both are suitable only for short-term storage.

Water vapour at +4° C.—When an eye is preserved in this medium it is suitable for an optical graft for up to 3 days; it is a method which is popular in the United States of America, where there is a rapid turnover of material, but it has the disadvantage of being useful only for a short period.

Liquid paraffin at +4° C.—By this method (Bürki, 1948) corneal graft material for sight restoration may be preserved for up to 6 days, and even longer when the material is to be used for a therapeutic graft. Disadvantages are that it is difficult to dissolve antibodies in the oily medium, and that at operation the oil tends to cling to the graft. Nevertheless, it has served as a routine method for many years at several clinics Sachs (1957) has modified this method by formulating a preservative medium composed of antibiotic and nutrient material, together with an indicator which denotes the sterility or otherwise of the eye. The medium is prepared in 500 millilitre quantities and the ingredients are added to a sterile bottle in the following order: Intradex, 200 millilitres; dextrose solution, 200 millilitres, phenol red solution, 20 millilitres, chloramphenicol, 0·5 gramme; streptomycin, 0·5 gramme; and melted nutrient agar, 80 millilitres.

At East Grinstead this medium has been found very useful in the transport of eyes to the Bank; if the phenol red indicator has a yellowish tinge on arrival the eye is discarded as being contaminated. The medium is not suitable for the long-term preservation of eyes.

Long-term preservation

So far then the most suitable and safe method of preservation does not extend beyond 7 days, and this period of time is not long enough. Stimulated by the work

of Polge, Smith and Parkes (1949), who showed that spermatozoa could be preserved for long periods at a low temperature, the attention of ophthalmic surgeons seeking a long-term method of preservation has naturally turned in this direction.

Research into three methods of long-term preservation is under way in three different countries. In the United Kingdom the graft material is soaked in 15 per cent glycerol for 1 hour before freezing it to −79° C., at which temperature it is preserved surrounded by carbon dioxide snow In the United States of America the corneal graft is preserved in 15 per cent glycerol and dehydrated, thereafter it is preserved at room temperature *in vacuo* In France the corneal material is desiccated by lyophilization and freezing to a low temperature.

The method of Polge, Smith and Parkes.—Eastcott and his colleagues (1954) reported that this method was suitable for the preservation of material for partial-thickness grafts but that the results with full-thickness grafts was less satisfactory. Billingham and Rycroft (1955) also described the application of the method and stated that "the long-term preservation of corneal donor material at very low temperatures still awaits a satisfactory solution" Rycroft (1957) published a report of a successful corneal graft in which the graft had been preserved at −79° C. for 4 weeks Vision was restored from "perception of light" to 6/12 It was noted, however, that the behaviour of this graft was different from that of fresh material; there was a long period of oedema before complete transparency of the graft was obtained

Storage in vacuo.—King (1957) considered that freezing damages the cell of the graft and described a method by which the corneal tissue is soaked in 95 per cent commercial glycerol and then dehydrated *in vacuo.* The tissue is subsequently preserved in sealed glass tubes at room temperature By this method the material is much more convenient for transportation than when it is preserved at −79° C. surrounded by carbon dioxide snow.

Rapid freezing and lyophilization —In France, Henaff and Rey (1957) favoured preservation by a rapid freezing and lyophilization; the graft material is dehydrated and desiccated *in vacuo*, thereafter, it is preserved in nitrogen in sealed flasks. Payrau (1958) reported successful heterografts with material preserved by these means and claimed that the antigen property of the graft is thereby much reduced.

Summary —A reliable long-term method of graft preservation is not yet available, though lamellar grafts can safely be obtained from material preserved at low temperatures over several weeks Successful results have been reported in the case of full-thickness grafts preserved in this way but sufficient consistency in these results has not yet been obtained to justify routine application; further research is necessary

The biological behaviour of the corneal graft

A final decision as to the fate of the individual components of a corneal graft has not yet been reached It would appear that the collagen structure of the graft remains integrated with the host cornea, but that the cells are replaced by migration from the host, there is certainly no mass necrosis of the graft

From the clinical point of view it is probable that the endothelium is the most

important structure of the graft in relation to optical clarity. It must be remembered that the true measure of success of a corneal graft is perfect transparency, regular contour and visual improvement; mere anatomical continuity is not considered a satisfactory standard The antigen reaction of the cornea continues to be studied. Maumenee (1951) has shown that a second corneal graft performed in a rabbit within 8 weeks of a first corneal graft, invariably causes clouding of the first graft, whereas, if the second graft is performed at a later period, the first graft remains clear and unaffected. This phenomenon is well known in connexion with skin grafts and has been called the "second set phenomenon". Maumenee suggested that this indicates that in rabbits the stromal cells have been replaced by cells from the recipient, or that the tissue has become acclimatized to the recipient animal. More recently, Streiff and Shapiro (1958) working with intralamellar grafts in rabbits have shown that two simultaneous grafts on both eyes regularly provoked an inflammatory action, but that this did not occur if the donor grafts were deprived of the epithelial layer. Also, a graft of epithelium alone provoked a similar reaction, whereas a graft of corneal parenchyma alone showed no reaction.

Just why the cornea should behave differently from other tissues in the production of an antigen response is not known. For example, a homograft of skin will necrose in 6 weeks unless the skin be taken from an identical twin. The cornea does not behave in this fashion and this may be due to the low antigen dose, since there are few cells in a corneal disc of 5 millimetres in diameter, or it may be because there is an absence of blood vessels in the corneal material. Probably both reasons are valid but the problem still awaits elucidation.

CONCLUSION

The conclusion in 1959 is that the corneal graft operation has become an essential component of modern ophthalmic surgery. It represents a major advance, along with the surgery of retinal detachment, in the treatment of blindness in our century. This fortunate state is due to the initiative of surgical pioneers, the antibiotics of the biochemist, the skill of the instrument makers, the investigations of the biologists, and the faith and trust of the patient.

"Think what a precious thing you work upon".

George Baker (1540–1600)

APPENDIX

CORNEAL GRAFTING ACT, 1952

(15 & 16 Geo. 6 & 1 Eliz 2)

An Act to make provision with respect to the use of eyes of deceased persons for therapeutic purposes. (26th June, 1952)

Be it enacted by the Queen's most Excellent Majesty, by and with the advice and consent of the Lords Spiritual and Temporal, and Commons, in this present Parliament assembled, and by the authority of the same, as follows —

1. **Removal of eyes of deceased persons**—(1) If any person, either in writing at any time or orally in the presence of two or more witnesses during his last illness, has expressed a request

(a) ... so dealt with after his

(b) ... eceased objects to the

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or cremation.

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(8) In the application of this section to Scotland for subsection (4) there shall be substituted—

"(4) Nothing in the foregoing provisions of this section shall authorise the removal of eyes from a body in any case where the procurator fiscal has objected to such removal "

2. Short title, extent and commencement—(1) This Act may be cited as the Corneal Grafting Act, 1952.

(2) This Act shall not extend to Northern Ireland

(3) This Act shall come into force three months after the passing of this Act.

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ABSTRACTS RELATING TO CORNEAL GRAFT SURGERY

Corneal grafting

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homoplastic material. The former is always associated with failure of the graft either by *complete rejection or, more rarely, by replacement of the transplant by opaque fibrous* tissue from the host. The increase in frequency of performance of the operation is the result amongst other things of the use of antibiotics, the development of exquisite instruments, the availability of donor cornea from cadavers and the increasing experience of the most suitable case for corneal grafting. Leigh considers the choice of case very important if dislodgement of the graft by slight trauma, such as eye rubbing or lid squeezing, is to be avoided. No upper age limit need be set providing the patient's general health is good and chronic cough absent. The author discusses the supply and storage of donor material There is a division of opinion over the choice of anaesthetic. While many favour a local one the use of present-day general anaesthetics is relatively safe with small risk of post-operative vomiting. He considers the essential principle for

Contributions to technique

CASTROVIEJO (1957) presents three contributions to keratoplasty. The numerous devices to maintain the graft in position emphasize the importance of maintaining the borders of the graft and recipient cornea in good apposition during early cicatrization The author has used conjunctival flaps, continuous overlying and direct sutures. The

... the last two being invaluable for corneal surgery.

... and transferred to the patient's eye.

This, however, left a dense opacity and often vascularization ...
post-operative course. The author has modified the procedure, using a fine needle and a current of low intensity and only involving the superficial corneal layers. The fulguration begins at the apex of the conus and is continued concentrically until the curvature is ... that of a normal cornea An incision is made outside the

layer is then possible. Once clear tissue has been reached, the lamellar graft, increased to the requisite thickness, is placed in its bed and sutured.

Three unusual cases

RYCROFT (1957) describes three unusual corneal grafts Case 1 was a contralateral

valescence was uneventful and the visual acuity in the right eye became 6/9 (unaided). No discomfort had been experienced over 2½ years post-operatively. The graft remained quite clear without vascularization Case 2 involved use of donor graft preserved at −79° C. for full-thickness keratoplasty. The patient aged 51 years had binocular vision of 1/60 which could not be improved by the use of contact lenses There was a dense white central leucoma in the right eye and a less dense grey one on the left side. A 5 1-millimetre full-thickness keratoplasty was performed on the right eye, the donor graft coming from a cadaver eye excised 4 hours *post mortem* and preserved at −79° C for 4 weeks. Post-operatively the graft cleared slowly and 2 years later it was 100 per cent clear, the fundus being well seen and visual acuity without correction being 6/24 to 6/18 Case 3 was a research fellow in chemistry aged 26 years who sustained multiple eye perforations when a glass retort exploded Both corneas showed many circular grey opacities and

6/60. This could be improved to 6/18 with a telescopic lens

Preparation of corneal grafts

Lyophilization

and the flasks are hermetically sealed *in vacuo* Reconstitution is complete at the end of an hour Results show that only the rapidly frozen grafts are permanent and transparent The histological structure and substructure are perfectly preserved but the constituent proteins are altered, the tissue losing much of its antigenic property. Both homografts and heterografts have been used with successful results. Rabbits' corneas, grafted into the eyes of dogs, are intact and transparent after several months Clinical trials in man are giving satisfactory results.

Lyophilized homografts and heterografts

Clinical results

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5 others behaved like fresh grafts, some remaining transparent, others becoming more or less opaque. In a keratoplasty, performed for an almost total opacity, the graft (lyophilized 3 days before) was clear at first but rapidly underwent vascular invasion. The keratitis reappeared on the graft and the eye virtually assumed its pre-operative state. Central lamellar keratoplasty was performed on a patient with a highly vascular traumatic keratitis. The graft remained

was later

s and all 5 show that properly prepared

of grafts is to be avoided. The author has twice used pigs' corneas for invading pterygia limited to the nasal sector of the cornea. In one case, the graft remained intact for 27

explains the rejection. Keratoplasty, again using a dog's eye, was performed on a large corneal scar resulting from burning by hydrochloric acid. The graft was rapidly incorporated but vascular invasion of the periphery occurred. After 4 months, this began to regress and the graft and neighbouring cornea gradually to clear. After 7 months, the fundus could be examined. The above observations are submitted without further claims or conclusions.

Partial lamellar corneal grafts

Survival of stromal cells

KORNBLUETH and NELKEN (1958a) report on experiments in which partial lamellar corneal grafting was performed on rabbits. A corneal disc was removed with a Franceschetti trephine and sutured into the wound made by a similar trephining operation on another animal. Clear grafts were obtained in only 21 per cent of a first series of 94 eyes. With improvement in the surgical technique, however, successful results were obtained in 55 per cent of 52 eyes. Usually the successful grafts showed a minimal degree of oedema for the first 3 days, but oedema was more pronounced in those grafts which eventually became cloudy. Good results were always encountered when grafts remained clear for 7–10 days after the operation. Slit-lamp examination of the recipient corneas revealed that superficial blood vessels had reached the edges of the wound within 7 days. Later, the

nuclear leucocytes.

Donor-recipient sensitization

KORNBLUETH and NELKEN (1958b) report on corneal-transplantation experiments in rabbits. Pairs of animals were selected and lamellar discs were exchanged. The discs were inserted near the limbus in order to facilitate blood-vessel invasion. In the majority of cases clear lamellar grafts were obtained and the grafts continued to remain clear for as long as 7 months. Histological examination revealed that the epithelium had survived and that the stromal fibres had not been replaced. During the series of experiments pieces of skin from the abdomen of the donor rabbit were inserted into the abdominal wall of the recipient animal. It was found that when corneal grafting was performed 7–14 days prior to skin implantation clear grafts were obtained in only 41 per cent of cases. Substantially similar results were obtained when the corneal grafts and skin implants were inserted at the same time. In contrast, all the corneal grafts remained clear when the

eye operation was performed 2 weeks prior to skin implantation. Temporary clouding occurred when the antigenic dose was increased by the insertion of a second corneal graft. Donor recipient sensitization led to a high percentage of opacities in partial perforating homologous corneal grafts The authors point out that the aqueous humour of the anterior chamber is a site of antibody formation, and the relative low percentage of late clouding of lamellar grafts may be due to lack of contact between the donor cornea and the aqueous humour.

Corneal heterografts in rabbits

The steadily increasing and unsatisfied demand for donor eyes for keratoplasty in recent years has led to the reinvestigation of the possibility of using animal or avian

possibly because of less superficial vascularization in interlamellar than in lamellar grafts. There was better overall tolerance of rabbits' eyes for avian donor tissues as compared to mammalian tissues, suggesting that the farther apart phylogenetically the two tissues, the less likelihood there is of the development of a donor recipient reaction. It is possible that avian tissues might be better tolerated than mammalian if used for human heterografts.

Interlamellar corneal homografts

Immunity studies in rabbits

Basu and Ormsby (1957b) studied immunity with interlamellar corneal homografts in

subsequent development of the typical reaction At the time of the reaction, a secondary group of more superficially placed blood vessels developed and invaded the graft. Where grafting was performed with donor cornea from the same species reactions occurred in 30 per cent, but where simultaneous grafting of related skin was undertaken the reaction

side

Use of preserved ocular tissues for transplantation

after treatment with glycerin. When the graft is required for lamellar keratoplasty the tube is opened with an electric tube cutter and the liquid is decanted. Then the cornea is

rehydrated in an ant
tion is less lik
cases of active
enhances the

Viability of frozen corneas

DRAHEIM and his colleagues
mined in tissue culture. Corneas
placed in a saline solution cont . The specimens were frozen by storage in solid dry-ice at a temperature of − 79° C. At various intervals the specimens were thawed rapidly, explanted and then incubated. Fresh corneas
in order to serve as controls. With
were viable. There was a
changes were observed
physical appearance of t after a period of 1 month, and wrinkling was often observed after 6 months. At the latter stage migration had either decreased or ceased. Of 5 corneas frozen for 6 months migration was observed in 3 cultures. When various concentrations of glycerol were employed it was found that glycerol, 10–25 per cent, had produced the least change in the structure
of the tissues. In a third series of
pared with a technique in
of the cornea resulted whe
viability. The authors poi
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freezing gives ris
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Stored corneas

Electrophoretic studies

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the protein changes and
trials should be made

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PLASTIC SURGERY OF THE SOUND CONDUCTING MECHANISM

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INTRODUCTION

The emphasis in temporal bone surgery has moved from the procedures aimed at saving life to those designed to preserve and improve hearing The advent and development of chemotherapy and antibiosis have reduced the extensions of suppuration in the middle ear cavity and the consequent dangers to life and health, but have not yet eliminated persisting infection which, if it is responsible for nothing worse, seriously reduces the hearing capacity of a great many individuals.

The use of antibiotics as an operation cover and the development of temporal bone surgery under magnification, giving such beneficial results in otosclerosis and other non-suppurative conditions, led to the introduction by Moritz, Wullstein and Zollner (Moritz, 1950) of improved methods of treating suppurative conditions.

It had already been realized that much more complete exenteration of diseased tissues could be achieved through the use of the operating microscope and this improved technique led to the development by the three workers in Germany of methods of repairing the damage done to the sound-conducting mechanism of the middle ear.

PHYSIOLOGICAL PRINCIPLES

Movement of the basilar membrane, upon which hearing depends, occurs when the proportion of sound energy entering one window of the internal ear is greater than that entering the other. This is well seen in the normal ear when the greater proportion of the sound energy reaches the inner ear through the conducting mechanism of the drumhead and ossicles. Little reaches the round window because of loss of energy in transference from the tympanic membrane to the air in the middle ear and again from the air of the middle ear to the round window membrane.

In suppurative disease of the middle ear, hearing loss results because of a reduction of energy transmitted through the conducting mechanism Hearing loss also results when a perforation of the tympanic membrane permits more sound energy to reach the round window thus reducing further the difference in the energy reaching the two windows.

In a radical mastoid cavity, for instance, the sound energy reaching the oval window is reduced and that reaching the round window is increased so that the energy-difference between the two windows is diminished and severe deafness results This difference can be increased, and the hearing improved, by applying a pledget of cotton wool into the round window. This is the so-called artificial drum effect which has been in clinical use for many years.

Reparative measures intended to improve the hearing, where there is interference with conduction, have two aims· (1) to increase the total sound energy reaching the oval window, and (2) reduction of sound energy reaching the round window which increases the proportion of sound energy entering the oval window A third method is a combination of these two.

SURGICAL PRINCIPLES

The surgical treatment that has been worked out with these aims in view consists of a number of separate procedures

Elimination of active inflammation

The first is the elimination of active inflammation and its products, leaving an ear or a cavity in the temporal bone which may be expected to remain healthy Where there is a central perforation, it will be possible in the majority of cases to achieve this by vigorous local treatment which includes appropriate antibiotic therapy Where the perforation is marginal or attic or where granulations or cholesteatoma indicate bone disease, it is often not possible to achieve more than temporary improvement by local treatment and the use of antibiotics. Operation should be carried out when the maximum improvement possible by these means has been achieved Exenteration of the mastoid antrum and cells is performed. The outer attic wall is completely removed and the facial ridge is severely lowered, particular care being taken to eliminate granulations overlying the bend of the facial nerve above and behind the oval window All diseased tissue is removed without consideration for the subsequent repair which must be planned to make the best use of healthy tissue remaining

Re-creation of a tympanic cavity

The second procedure is to re-create a tympanic cavity which is completely shut off from the outside air except through the lumen of the eustachian tube which must be patent This new tympanic cavity may occupy the same space as the original one, it may occupy only the lower half, or it may consist of a narrow tunnel connecting the eustachian orifice and the niche of the round window The choice of one of these three cavities depends on whether the ossicular chain is intact and functioning, when the whole tympanum is reconstructed, or whether the chain is irretrievably broken and only the stapes can be used. In this case a smaller tympanum is made which does not include the epitympanum but extends from the

level of the intratympanic portion of the facial nerve downwards Where the stapes can no longer be used for conducting sound, the hypotympanic tunnel is constructed so that the round window is included in the new cavity but the oval window is not.

The new cavity must contain air which can be replenished from the outside through the eustachian tube—the continued patency of this is therefore essential. To procure this air-filled cavity the tympanic membrane must be repaired and this is done by applying a skin graft to the outer aspect of the drumhead—or what remains of it. The graft must cover a wide area of the drumhead and also a part of the external auditory meatus The graft must consist of whole thickness skin in the part which covers the perforation and the remaining portion of the tympanic membrane, but should be thinned down to a half thickness or less in the part which is in contact with the walls of the meatus If the graft is to live it must receive nourishment from the tissues of the host. To achieve this object the surface layer of the epidermis of the bed of the graft—tympanic membrane and skin of meatus —must be dissected off so that plasma can flow into the graft and eventually new vessels or plasma channels may be formed.

Utilization of ossicular chain remnants

The third part of the manoeuvre consists of the utilization of what remains of the ossicular chain, or its rejection if no longer usable. The suppuration, which has led to the damage in the middle ear and to the necessity for the plastic procedures, usually causes the destruction of the incudo-stapedial joint and necrosis of the terminal part of the lenticular process of the incus This results in considerable deafness as no sound can pass through the ossicles to the oval window. Attempts have been made, by partially dislocating the incus, to bring the stump of the incudal process into contact with the head of the stapes, but this is a difficult manoeuvre and is not often successful The other common site for bone damage is the bony mass consisting of the head of the malleus and the body of the incus. A moderate degree of erosion of the ossicles may leave enough of the two bones —if they are held together by their original ligaments or by new fibrous tissue— to enable sound to be conducted through to the stapes. In such case the ossicles are left and the whole tympanic cavity is reconstructed by plastic closure of the perforation.

If the loss of continuity of the ossicular chain is irreparable, the remains of the incus and at least the head of the malleus are removed. If removal of the handle of the malleus would cause considerable loss of useful tympanic membrane it may well be left in position If the stapes is intact and its footplate is still capable of movement in the oval window the skin graft forming the new tympanic membrane is laid in contact with the head of the bone and a new conducting mechanism which is comparable to the columella of the bird—a single bone linking the tympanic membrane with that of the oval window—is formed. The beauty and complexity of the song of many birds indicates the remarkable efficiency of this mechanism.

Where the head and crura of the stapes have been destroyed, and only the footplate remains, the procedure to be followed depends on the mobility or immobility of the remnant of the stapes in the oval window.

If it is mobile it is not covered by the skin graft, and an hypotympanic tunnel is constructed which encloses the round window, in an air-filled cavity.

If the stapes is fixed in the window and cannot be readily mobilized it may be covered by a skin graft, the hypotympanic tunnel constructed and a fenestration of the external semicircular canal carried out.

The success of the new tympanic cavity depends largely on the integrity of the mucous membrane lining the cavity. This may be septic, it may be chronically thickened, it may be polypoid, or it may be destroyed Removal of diseased portions under magnification may in most cases be sufficient, but in those cavities in which the membrane is largely destroyed it is wise to replace it by a more healthy area of mucosa The bulge of the promontory is the usual site for severe destruction of mucous membrane and it is possible to cover this area by a piece of healthy mucous membrane which may be removed from the interior of the maxillary antrum or, less satisfactorily, from the inside of the lip.

PRE-OPERATIVE INVESTIGATIONS AND TREATMENT

Success or failure in the elimination of infection before operation will greatly influence the outcome of the operation, and it is usually necessary to carry out pre-operative treatment in hospital for a period, the length of which will depend on the progress made. Antibiotics are used locally and systemically under bacteriological control, and the operation is carried out under appropriate antibiotic cover Any source of infection in the nose, sinuses, nasopharynx or pharynx must be treated The eustachian tube must be functionally patent. If not freely patent it must be regularly inflated and if necessary dilated by means of a gum-elastic bougie until the normal method of replenishing tympanic air through the tube is re-established

Where it is proposed to close a perforation without inspection of the ossicular chain it is essential to know that the chain is intact. Where the perforation is small, it can be closed temporarily by a patch of thin paper An audiogram will then show the improvement in hearing that can be expected from operative closure of the perforation. Where the perforation is large the acoustic probe must be used The simplest type of probe is a bone conduction hearing aid receiver with a rigid steel probe bolted to the case. Power is supplied through one of the usual pure-tone audiometers at known frequencies and intensities Other forms of probe include that designed by Bennett (1956) in which the sound is carried by a flexible wire probe resting in contact with the diaphragm of an air conduction receiver and another type developed in the laboratories of the Institute of Laryngology and Otology which has a rigid probe fixed to the diaphragm of the same type of receiver

Threshold measurements are made with the probe resting on (1) the malleus, (2) the promontory and (3) the stapes where it is exposed The tests are carried out at three frequencies—500, 1,000 and 2,000 cycles per second. Where the chain is intact hearing on the malleus will be better than that on the promontory by about 30 decibels Where the chain is broken, hearing on the promontory will be better than that on the malleus Intermediate figures, which are unusual where the perforation is central, indicate adhesions limiting the mobility of a chain which

is not actually broken. When the probe can be applied to the stapes, it will be found to indicate the same threshold as on the malleus where the chain is intact. Where the chain is broken, a mobile stapes will give a reading about 30 decibels better than the promontory which in turn will be better than the malleus.

It is now well known that good hearing in an ear with cholesteatoma may be due to transmission of sound through the cholesteatoma. After removal of the cholesteatoma a reduction of acuity of hearing, which may be of considerable degree, is noted. The fact that sound is being conducted through cholesteatoma may be recognized from readings made with the acoustic probe. Sounds of low frequency pass readily through the rubbery mass of cholesteatoma and it is found that at 500 cycles per second the hearing on the malleus is about 30 decibels better than on the promontory, which is the normal relationship. Sounds of higher frequency are not so well transmitted and therefore as the frequency of the test tones is increased, transmission through the mass of cholesteatoma becomes progressively poorer, until at 2,000 cycles per second the hearing on the malleus is the same as that on the promontory, the transmission suffering by about 30 decibels. These differential results according to the variation in frequency are indicative of a conducting medium such as cholesteatoma, but not bone. The test can be carried out with but slight discomfort in the majority of patients. Local anaesthesia is better avoided as this may affect the internal ear with temporary reduction of cochlear function and even with vertigo and vomiting.

Skin graft

The defect in the outer wall of the tympanic cavity was originally closed by a full thickness graft, usually obtained from the skin behind the ear and below the hairline (Wullstein, 1951) This skin is relatively hairless, it is supplied only slightly with elastic fibres and has no great tendency to curl up. If a retro-auricular incision is used for access to the middle ear cleft, an appropriately shaped piece of skin may be removed at the same time The gap left after removal of this skin can readily be closed if a wedge of subcutaneous tissue is removed with the skin. If this is done, it is rarely necessary to undercut the skin edges. In any case the scar left by the removal of a piece of skin in this region is inconspicuous and can easily be hidden by the hair Every particle of fat is removed from the skin by means of scissors. The graft is then applied with its raw side towards the prepared drum and adjacent meatus in the case of myringoplasty or similarly to form the new outer wall of the tympanum and to line the adjacent part of the cavity.

It has been found that a full thickness graft sets up considerable reaction in the cavity: this takes a long time to resolve and may lead to secondary infection which leads to destruction of the graft It is also difficult to fit a full-thickness graft neatly into the somewhat acute angle between the anterior wall and floor of the meatus and the tympanic membrane or the inner tympanic wall Zöllner (1951) limits the amount of full-thickness skin to that forming the outer wall of the tympanum, the remainder of the graft being half thickness or less. This graft may be satisfactorily removed from the medial aspect of the upper arm. The skin in this region has advantages over the retro-auricular area in that it is thinner and

more supple, it is even more sparsely supplied with hairs and elastic fibres than that over the mastoid process. The graft is cut with an ordinary straight razor and is so arranged that only the central part is full thickness whilst all the peripheral part of the graft is about half thickness or even less (Fig 74). A slightly larger area of split skin is removed than is required for the ear, and a portion is separated and applied to that part of the area from which the full-thickness skin has been removed, thus reducing scarring to a minimum. The graft itself can be applied to the denuded area of the remainder of the drumhead and of the external meatal wall, and this thin part of the graft can be readily moulded to the shape of the cavity, particularly in the difficult antero-inferior angle of the tympano-meatal sulcus.

To facilitate the cutting of a graft a metal plate with a circular or oval hole has been devised. This can be applied to the skin surface under such pressure that the skin bulges through the opening. By using an ordinary razor and sliding it along the surface of the plate a whole thickness or a partial thickness may be cut. The thickness of the graft may be varied by changing the pressure on the plate and thus presenting more or less skin. In this way good grafts may be obtained but it is not possible, by this method, to cut a graft which is whole thickness in the centre and still has a considerable margin of split skin surrounding the thicker part

TYPES OF OPERATION

Myringoplasty

This operation is indicated where deafness is due to a defect in the conducting mechanism, which consists of a central perforation in the pars tensa of the tympanic

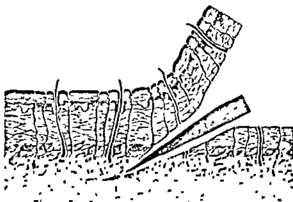


FIG 74 —Cutting a mixed split skin and full thickness skin graft from the inner aspect of the upper arm The central full thickness part will form the outer wall of the tympanum

membrane There should be no evidence of bony disease in the form of granulations or cholesteatoma and the ossicular chain must be shown to be intact by the acoustic probe or by audiogram after the application of a temporary patch Closure of a central perforation is also carried out with the object of preventing recurring infection of the middle ear through the eustachian tube, following any attack of nasal or postnasal catarrh Closure of the perforation also permits the

individual to bathe and to swim without the risk of reinfecting the middle ear through the external meatus and the perforation. The ear should have been dry for several weeks before operation.

Operation

Using sixfold magnification with the operating microscope, the epithelial surface of the tympanic membrane is elevated to provide a bed for the graft. The elevation should be extended for 5 millimetres peripheral to the margin of the perforation. This will usually necessitate the inclusion of a portion of the external meatal wall in the bed for the graft. Elevation of the epidermis is carried out by making an incision through it at the appropriate distance from the edge of the perforation and then, by means of separators, the outer layer is dissected towards

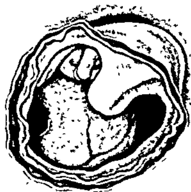


FIG. 75.—Myringoplasty—incision of the skin of the meatal wall and elevation of the flap medially. (From *Operative Surgery*. Edited by C Rob and R. Smith. London, Butterworth.)

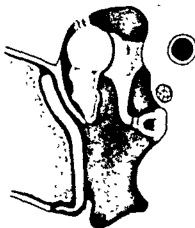


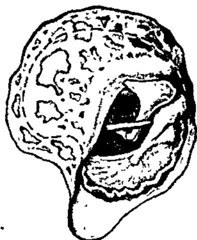
FIG. 76.—Myringoplasty—graft closing defect in the tympanic membrane. (From *Operative Surgery*. Edited by C. Rob and R. Smith London; Butterworth.)

the perforation (Fig 75) The pedicle flap so formed may be turned into the perforation to close it, trimming it to shape if necessary. A graft, cut from the inner aspect of the upper arm, as previously described, is applied so that the full-thickness skin covers the whole drum and the split skin portion covers the bared meatal wall. It is inserted into the ear, wrapped round a small pledget of cotton wool (Zöllner, 1951) which is then removed and the graft is fitted on [illegible] held in place by absorbable sponge and by an outer [illegible] with bismuth, iodoform and paraffin [illegible] may be gelatine foam [illegible] d before use in a [illegible] d in 10 millilitres [illegible] handle. If it is le[illegible] (Fig 76).

[illegible] and easy to [illegible] disintegrates, liquefies and is dissolved

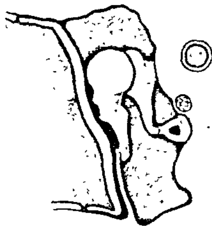
Epitympanomastoidectomy with skin graft

This operation is used where the ossicular chain is intact, but where the presence of bony disease is shown by marginal or attic perforation, granulations or cholesteatoma. Attic antrostomy is carried out in the usual way with removal of the bridge and outer attic wall Great care must be taken to avoid damage to the ossicles, particularly the attachment of the short process of the incus, when the facial ridge is being lowered. The outer meatal skin is used to form a Körner or Ballance flap which widens the meatal opening and allows adequate post-operative



Butterworth)

FIG. 77.—[illegible] graft—the [illegible] skin graft. [illegible] provide a [illegible] *Surgery* Edited by C Rob and R Smith. London; Butterworth)



treatment and observation of the cavity to be carried out The skin of the inner meatus is kept intact at this stage The operating microscope is now used to ensure that all diseased bone with granulations has been removed, and to inspect the ossicles These can be brought fully into view by elevating the meatal skin and fibrous tympanic ring and turning them forwards with the posterior half of the drum, or what remains of it The ossicles are retained if they are intact All granulations and cholesteatoma must be removed from the ossicles and this will often mean sacrificing the incus and the head of the malleus, particularly where there is extensive cholesteatoma deep to the ossicles. Mucous membrane which is moderately swollen should be retained as it will recover once the infection is brought under control The incudo-stapedial joint should be most carefully

examined, as the lenticular process of the incus is frequently replaced by a band of fibrous tissue or granulation tissue. When the ossicular chain has been inspected and found to be intact and free of disease, and when transmission has been demonstrated at the round window, the formation of the new tympanic cavity can be undertaken. Where there is a small attic, or postero-superior, perforation, the middle ear can occasionally be closed off by using the skin of the inner end of the meatus as a fenestration type tympano-meatal flap which is turned up over the ossicles on to the cavity walls. The perforation may be closed by using a small fold of the flap. Usually it is necessary to use a graft which extends from the inner end of the external auditory meatus, over the drumhead and on to the adjacent walls of the cavity. Where a graft is used the inner meatal skin tube should be incised longitudinally in the antero-superior angle, and the skin turned back to cover the facial ridge To create a bed for the graft it only remains to remove the epithelial layer of the drumhead and adjacent 5–10 millimetres of the meatus, as for myringoplasty (Fig 77) The graft is cut from the inner aspect of the upper arm, full thickness to cover the drum and ossicles and split skin to cover the prepared meatal wall and the adjacent parts of the mastoid cavity. After haemostasis the graft is applied taking great care to avoid any turning in of the edges of the graft It is held in place by an inner pack of absorbable sponge and an outer pack of B I.P.P (Fig. 78).

Columella type tympanoplasty

This operation is used where there is interruption of the ossicular chain but where the stapes is still intact and mobile. Interruption of the ossicular chain is usually caused by erosion of the long process of the incus, but it may be necessary to break an anatomically intact chain by removal of the malleus and incus where these are firmly bound by adhesions or are irretrievably involved in cholesteatoma or granulations. Disease in the mastoid process is removed in the usual way with removal of the bridge and outer wall of the attic The facial ridge is severely lowered to bring its surface as near to the plane of the head of the stapes as possible. The attic is completely exenterated and all mucous membrane down to the horizontal part of the facial nerve is removed The microscope is then used to examine the stapes for mobility, and for the presence of granulations which should be removed, and for adhesions which should be divided. It may be necessary to divide the stapedius tendon so as to be able to clear the posterior part of the stapes completely. A new tympanic cavity is formed which extends from the tympanic ring to the horizontal part of the facial nerve. The outer wall is formed by a skin graft or occasionally by a tympano-meatal flap which in either case is laid in contact with the head of the stapes The outer layer of the tympanic membrane is removed with the epithelium of the adjacent meatus to form a bed for the graft in its lower part. The skin graft is cut with a full thickness portion large enough to extend from the ridge of the horizontal portion of the facial canal to the tympanic ring with surrounding split skin to fit on to the bared meatus, into the attic and into the adjacent part of the mastoid cavity. The graft is held in place with absorbable sponge and an outer pack of B I.P.P (Fig 79).

Total tympanoplasty

This operation is applicable where the ossicular chain is disrupted and where the stapedial crura have been destroyed, but where the footplate is mobile or can be mobilized by removal of adhesions. The aim is to create an air-filled tunnel connecting the eustachian tube with the niche of the round window. The disease in the mastoid bone is removed in the usual way along with the whole outer attic wall, and severe lowering of the facial ridge. Remains of the ossicles and all granulation tissue are removed. With magnification the region of the oval window should be inspected. If the mucosa is normal, it will be possible to demonstrate the mobility of the footplate If the mucosa is thickened or if there are granulations or adhesions the footplate is exposed. This is best done by elevating the mucosa on the horizontal part of the facial nerve canal downward and approaching the oval window from above and in front. The footplate is frequently immobilized

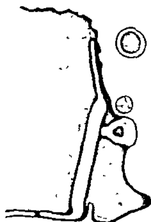


FIG. 79 —Columella type tympanoplasty—the tympanic cavity has been closed by a skin graft which is in contact with the head of the stapes (From *Operative Surgery* Edited by C Rob and R Smith London, Butterworth)

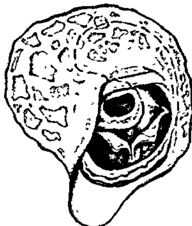


FIG 80 —Total tympanoplasty—elevation of mucosal flaps from the promontory. The meatus is being prepared for the reception of the skin graft. (From *Operative Surgery* Edited by C Rob and R Smith London, Butterworth)

by adhesions and these are removed until mobility is achieved. A T-shaped incision is made through the mucosa covering the promontory. The horizontal limb lies just below the oval window, the vertical one runs downwards along the line of the tympanic branch of the glossopharyngeal nerve to a point opposite the tympanic ring Triangular flaps are then elevated from the promontory and can be used to form the roof of the tunnel, the formation of which is greatly aided by the normal configuration of the hypotympanum (Fig 80) The remains of the tympanic membrane and the adjacent meatus are prepared for the reception of a graft which

is cut from the upper arm. A small full thickness area covers the new hypotympanic tunnel while the split skin portions extend on to the meatus and into the attic. The roof and outer surface of this tunnel consist of an inner lining of mucous membrane and an outer one of skin simulating the normal tympanic membrane. The stapes footplate lies free in the cavity either covered by normal mucosa or left uncovered. If the bare footplate is covered by full thickness or even by thin split skin graft, reduced hearing will result. The cavity is packed with absorbable sponge and an outer pack of B.I P.P (Fig. 81).

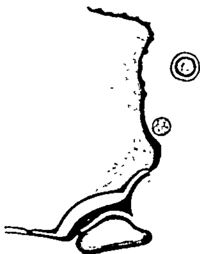


FIG. 81 —Total tympanoplasty—formation of an air-containing tunnel between the eustachian tube and the round window. (From *Operative Surgery*. Edited by C Rob and R. Smith. London; Butterworth)

Total tympanoplasty with fenestration of the lateral semicircular canal

If the footplate of the stapes is found to be fixed in the oval window and cannot be freed, the total tympanoplasty is carried out with creation of the tunnel as previously described The tunnel over the round window is essential, but the skin graft may cover the footplate and the oval window. After this has been done a fenestra is made into the external horizontal canal as in the operation for the relief of otosclerosis. This opening may be covered by the split skin portion of the graft and replaces in a functional sense the oval window.

The description of these types of operation is given as a guide only, and the actual operation in any particular case must be planned to make the best use of what remains of the conductive mechanism after the removal of all diseased tissue.

DRAINAGE OF TYMPANIC CAVITY

Zöllner has devoted much time and thought to the drainage of these new tympanic cavities especially in the fourth type of tympanoplasty, the formation of a tunnel between the eustachian orifice and the round window or minor tympanic cavity. His earlier technique of leaving a length of silk thread coiled in the hypotympanum and led out through the eustachian tube was not satisfactory and has been abandoned.

A fine polythene tube has been introduced into and retained in the eustachian tube to ensure its continued patency and drainage of the tympanum, but this has not been entirely satisfactory Zollner (1954) has therefore devised and constructed a malleable polythene tube of very fine bore which can be passed from the tympanic cavity through the eustachian tube to the nose. The tube contains a silk thread which projects beyond the end of the tube This thread is tied to the end of a eustachian bougie which has been passed and as the bougie is withdrawn the tube follows it and its end can be brought out through the nostril (Fig. 82)

The tympanic portion of this tube is curved through rather more than a third of a circle to lie along the floor of the tympanum between the opening of the eustachian tube and the niche of the round window. The open end of the tube lies immediately below the niche, and two or three small drainage holes are made in the curved part of the tube This will ensure drainage of serous fluid forming in the middle ear cleft

The tube is drawn through the eustachian tube towards the close of the operation before the graft is applied. It is led out through one side of the nose and eventually

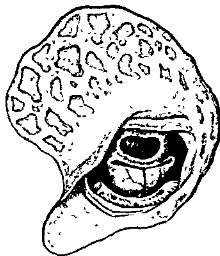


Fig 82 —Polythene tube inserted into the eustachian tube The terminal curved

after 2–3 weeks is removed by traction on the exposed end—the polythene being pliable enough to allow the curved portion to be withdrawn from the tympanum. Eustachian inflation is commenced immediately after this drainage tube has been removed

POST-OPERATIVE CARE

Antibiotic cover is continued for the first week of the post-operative period At the end of the first week the B I P.P pack is removed and replaced by a fresh one for a further 3 days The gelatine foam is allowed to come away gradually, and the meatus should be cleared of it by the end of 3 weeks To avoid introduction of infection the aim should be the least possible interference with the operation cavity.

Inflation of the eustachian tube should commence 2–3 weeks after operation. This should be by Valsalva's manoeuvre, while the tympanic part of the cavity is observed, preferably with magnification If Valsalva's method is unsuccessful, politzerization is used and if that fails eustachian catheterization is carried out Whichever method is used the effect on the tympanum must be observed. During inflation there may be some leak of air from the tympanum, usually posteriorly This should not lead to a cessation of inflation, since this must be repeated daily until the patient can easily inflate his new tympanum by Valsalva's method.

The success of tympanoplasty depends very largely on careful and patient post-operative care.

COMPLICATIONS

Recurrence of suppuration

It has been emphasized that infection in the middle ear cleft and its adnexa must be reduced, before and during the operation, to the absolute minimum possible in amount and in activity. The recurrence of active inflammation in the cavity within a few days of the operation may result in the displacement of the skin graft or even of its disappearance. Infection occurring at a later date or in a less active form may lead to a serous exudate or even an empyema in the new middle ear cavity Either of these may cause perforation of the new tympanic membrane or its eventual destruction. If the membrane survives it may become adherent in greater or lesser degree to the inner wall of the tympanum, obliterating the cavity and occluding both windows, or it may survive with one or more perforations Any of these events will effectually reduce or preclude the anticipated increase in hearing

Recurrence after myringoplasty

[illegible]

is performed in the meatus and tympanum When the infection has subsided [illegible] necessary to ascertain if the mastoid antrum and air cells have become involved—in which case exenteration will be necessary It will also be necessary to retest the hearing by means of the acoustic probe and therefore to determine the integrity or rupture of the ossicular chain Any further treatment will depend on the resolution of the infection and the condition of the ossicles. If an attempt is made to close the perforation by a graft, it will be more difficult again to denude the tympanic membrane of its epidermal layer, without destroying more of its substance. It may be necessary to fashion a pedicle graft from the skin of the meatus and turn this into the perforation before applying the free graft.

Recurrence after tympanoplasty

Where suppuration occurs after exenteration of the mastoid cells and bone and application of a graft, there is likely to be a total loss of the skin graft and a severe infection of the entire cavity with some degree of osteitis. This will entail a course of antibiotic therapy and dressing of the cavity and it may take many weeks to reduce the infection. When this has been completed it may be found that fibrosis

has reduced the permeability to sound of either or both of the windows. In such circumstances there is little likelihood of again creating a functioning middle ear and it is doubtful if any further plastic surgery is advisable. It may, however, be worth while relining the cavity with a split skin graft after thorough disinfection and, if required, some further removal of bone. If the acoustic probe tests indicate that the footplate of the stapes is mobile a further attempt may be made to construct the hypotympanic tunnel. With a fixed stapes a fenestration of the horizontal canal may be added to the reformation of the hypotympanic tunnel. It is doubtful if it is ever possible so to dissect out fibrous tissue from the windows as to enable them to function and in the majority of instances of secondary suppuration the achievement of a dry ear can be suitably supplemented by an aid to hearing without any further surgical disturbance.

Persistent exudate in the new tympanum

Where a less active form of inflammation occurs in the newly made tympanic cavity a serous exudate may be secreted probably without pain or discomfort, but with an increase of deafness This effusion may distend the new tympanic membrane and may cause its destruction or, more frequently, one or more perforations A persistent effusion or hydrops will reduce hearing and its eventual absorption will result in much intratympanic fibrosis, blocking the windows and reducing hearing capacity Reference has already been made to the necessity for the most complete removal of all infected and inflamed material and for the maintenance of eustachian patency Failure in either of these requirements may result in this exudation of serous fluid into the cavity It is equally important after the plastic operation to keep the eustachian tube open—first by Valsalva's manoeuvre, then by politzerization and if necessary by catheterization and inflation.

A persistent effusion may be diagnosed by a distension, which is not altered by use of a Siegle's pneumatic speculum, and in some instances by a visible fluid level If it does not respond quickly to eustachian inflation it is necessary to carry out paracentesis or an incision of the tympanic membrane In some persistent cases it may be necessary to repeat this incision on a number of occasions over many months before resolution is eventually gained Repeated drainage must be accompanied by eustachian inflation, which should be continued after cessation of effusion This treatment is similar to that employed for the serous exudate which follows non-suppurative inflammation of the middle ear cleft after certain types of influenza

RESULTS

The surgical treatment described has two objects in view The first is to achieve a dry healed ear and the second is to improve the hearing sufficiently to enable the patient to hear conversation without amplification

The first objective is reached in a greater proportion of patients than was the case when the tympanic and mastoid cavities were allowed to heal by granulation and epithelialization or were lined by a split skin graft. This is largely owing to the care taken to counteract the bacterial infection by chemotherapy and antibiotics, and to the possibility under magnification of eliminating more completely

all diseased tissue. The thicker skin graft and its method of application also help to obtain complete healing

The second objective—the restoration of useful hearing—is perhaps more difficult to achieve but considerable improvement is gained in a much higher proportion than in the former method of surgical treatment, and varies according to the extent of the damage to the conducting mechanism and therefore to the type of operation.

In myringoplasty (Type I) a return of hearing to normal is expected and occurs when the perforation is closed and the membrane regains its normal elasticity It falls short of normal in some cases and this may be because there has been some shortening of the handle of the malleus, or there is some fibrosis of the ossicles or the windows.

In epitympanomastoidectomy (Type II) with graft the healed dry ear is a very usual occurrence but the hearing recovery is variable. Normal hearing may result in favourable cases, but there are commonly adhesions around the malleus and

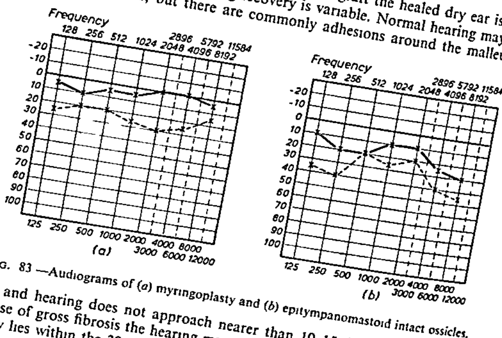


FIG. 83 —Audiograms of (*a*) myringoplasty and (*b*) epitympanomastoid intact ossicles.

incus and hearing does not approach nearer than 10–15 decibels to normal In the case of gross fibrosis the hearing may even remain worse than this figure, but usually lies within the 30 decibel range which gives useful hearing

In the columellar (Type III) operation it is anticipated that return to a hearing level of about 10 decibels from normal will result This loss of 10 decibels represents the difference between the hearing due to an intact ossicular chain and that resulting from a single rigid bone connecting tympanic membrane and oval window. It is possible, however, that in certain favourable instances this degree of hearing may be exceeded and in a few cases normal hearing may result. On the other hand adhesions around the footplate of the stapes may prevent the level of 10 decibels being reached.

In total tympanoplasty (Type IV and Type V), with or without fenestration, it is not anticipated that the hearing will be improved above a level of 25 decibels below normal Because of the many changes in texture of the bone and membrane

concerned it is found, as a rule, that the best result that can be achieved is the reduction of a hearing loss of 60 decibels or more to one of 40 or even 35 decibels.

If all the different types of suppurative otitis media and the five types of plastic operation are considered, it is found that 60 per cent of the ears become dry and have some improvement in hearing. The majority of the cases fall into the groups that require either Type I or Type IV operation—myringoplasty or total tympanoplasty.

Type I.—The majority of the grafts survive and an intact membrane results, with a return of hearing to normal or near in 60 per cent of cases.

Type II.—Relatively few patients are suitable for this type of operation, but a healed ear can be expected in almost every one

Type III.—Again relatively few patients are suitable and though healing occurs in the majority an improvement in hearing occurs in 25–35 per cent

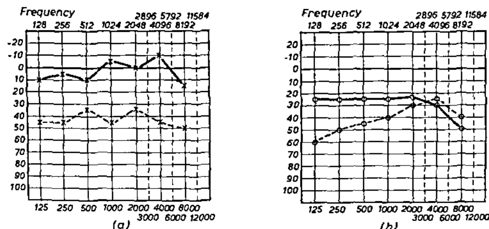


FIG. 84 —Audiograms of (*a*) columella type tympanoplasty and (*b*) total tympanoplasty.

Type IV.—The greater proportion of patients require this operation, namely, total tympanoplasty, and successful results, that is, a dry ear accompanied by an improvement of hearing, are achieved in 30–40 per cent.

Typical audiograms are shown from each of the first four types (Figs. 83 and 84).

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ABSTRACTS RELATING TO THE EAR, NOSE AND THROAT

Myringoplasty

MAWSON (1958) gives an account of an operation for the surgical reconstruction of the tympanic membrane. A piece of skin is obtained from an area on the posterior aspect of the auricle and mastoid process The full thickness graft is placed in normal saline at body temperature and the skin defect is repaired. The receptor area is viewed under a microscopical magnification of 10–16 times and a circular incision is made at the junction of the inner and middle thirds of the meatus. Dissection of the skin is continued inwards

is inserted into the graft and a purse-string catgut suture is tied round the mass so that the raw surface of the graft is everted. After the graft is introduced into the meatus in the desired position, the catgut suture is withdrawn and a plastic-sponge dressing is applied. Stitches and sponges are removed on the fifth day. In order to ensure that the graft is

best results were obtained when the pre-op
40 decibels. All grafts survived, but in 2 instances perforations occurred subsequently owing to otitis media. Temporary paralysis of the facial nerve was the only complication and the patient made a complete recovery after the sponges were removed.

Tympanoplasty

RICHTNER (1958) points out that tympanoplasty is indicated in the management of certain forms of chronic inflammation of the middle ear. Prior to the operation the middle ear is examined with special reference to the condition of the auditory ossicles and the type of perforation The hearing is tested with the pure tone audiometer. Sometimes speech audiograms are employed. Sonometric studies are of value in determining the condition of the ossicles and round window. If the ossicles are intact a modified radical operation is performed and a graft is applied to the tympanum and to the cavity created by the operation. When the long process of the incus shows a minor degree of destruction ... contact with the stapes. Care is ... us membrane of ... is important to avoid injuring the mucosal epithelium of the oss ... duced into the

... adopted ... defects ... of the ... of the ... for the mucous membrane is turned downwards so that ... The transplant is held in ... full thick- ... means of ... of more the cavum minor technique the author obtained ... than 10 decibels in 18 of 39 cases.

Basic techniques

Guilford and Wright (1958) describe the general principles and basic techniques of tympanic skin grafting. With regard to pre-operative procedures, suppuration is controlled by antibiotic therapy and aspiration of the secretions in the middle ear. Mastoidectomy is performed if a focus of inflammation fails to resolve Every attempt should be made to preserve the annulus, the mucosa of the middle ear and the function of the eustachian tube. Magnification with the Zeiss operating microscope is of value in detecting marginal perforations, squamous epithelium in the middle ear and cholesteatomatous debris. Tests of hearing function include the investigation of air conduction with a paper patch applied to the tympanic perforation The acoustic probe may be used in order to determine the efficiency of the ossicular chain. As for the surgical technique, local anaesthesia is effected with injections of Xylocaine and adrenaline. In operations for Type I cases skin flaps are prepared by incising the anterior and posterior canal walls. A three-fourths split thickness graft is cut with a "Weck" razor-blade from the non-hair bearing skin in the vicinity of the mastoid process The transplant is trimmed

the incudo-stapedial joint. Type IIB technique is used in cases of necrosis of the long process of the incus with loss of the true incudo-stapedial joint. The denuded tympanic remnant is raised from the annular sulcus and the bone is removed from the annular area in order to expose the incudo-stapedial joint; then a graft is applied to the long process of the incus and the head of the stapes For Type III the graft extends from the annulus to the floor of the attic and for Type IV the graft reaches the promontory. In Type V the graft covers the fenestra in the lateral semicircular canal.

Recent advances

epitympanic regions Beales and Hynes (1958) have implanted a living flap in the mastoid area supplemented by whole skin from the arm for tympano plastic reconstruction The gap behind the ear is covered by split skin Prior to the operation the activity of the disease must be reduced as far as possible by means of topical and systemic treatment

nylon thread within the catheter is
rotundum The thread is removed in
is performed daily by means of a n
ordinary syringe As for Type III, T
disease such as osteitis, granulation
cavity and mastoid process Irreversible disease includes cholesteatoma It is difficult, however, to effect the complete removal of cholesteatoma matrix from the cells in the hypotympanic and the peritubal regions. When possible the mucous membrane must be retained on the medial tympanic wall. The functional integrity of the ossicles and fenestrae should be tested and the operation should be performed in a relatively bloodless field

Results

PROCTOR (1958) reports on the outcome of 50 cases in which radical mastoidectomy was performed. Seventeen patients experienced some gain in hearing but only 6 patients showed an improvement of more than 30 decibels. In contrast, 49 of 75 patients benefited audiologically after conservative radical mastoidectomy. Satisfactory results were recorded in 3 of 4 cases after Type I tympanoplasty. When Type II tympanoplasty was performed gains of more than 30 decibels were recorded in 16 of 23 patients. In contrast, relatively poor results were obtained among patients treated with the Type III operation, for in these cases there was extensive destruction of the middle-ear structures. After Type IV tympanoplasty 7 of 17 patients showed a gain of 30 decibels. The outcome of the Type V operation was unsatisfactory. Probably the mucosal grafts were not always effective. Defects were also attributed to excessive fibrosis and to perforation of the grafts, presumably a complication of poor vascularity. The author concludes that Type I tympanoplasty has its place in the management of benign and dry perforations of the drum. As for Type II, with the refinements of microsurgery it is possible to eliminate some of the failures which are likely to be encountered when the conservative operation is employed. Type III and Type IV techniques afford the opportunity of restoring function in patients who formerly would have been subjected to radical mastoidectomy. In selected cases the Type V operation achieves sound protection for the round window and creates a new window open to the external ear. As far as possible the reconstructive operation should be performed in one stage, for multiple operations tend to precipitate fibrosis and adhesions.

Mastoid surgery

Use of post-auricular flap

BEALES and HYNES (1958) discuss rapid healing after mastoid surgery by the use of the post-auricular flap. An analysis of a large number of cases followed up over a period of years by several workers shows that about 20 per cent of all mastoid operations fail to heal completely. The data do not indicate the number of cases which, although apparently well healed, break down again, and this undoubtedly occurs in a considerable proportion of cases. The present authors have devised a method of obtaining rapid healing by providing all raw surfaces exposed during any type of mastoid surgery with a stable skin cover. The method involves no special training and prolongs the normal operating time by only about 20 minutes. The operation as used with tympanoplasty is performed under a modified hypotensive anaesthesia, using the "lytic cocktail"; hypotension is helpful but not essential. The method comprises: (1) preparation of a skin graft, of medium thickness, measuring about 10×5 centimetres; part of this is used as the graft for the tympanic cavity, and the remainder will provide skin cover for the secondary defect on the deep surface of the pinna at the end of the operation; (2) the raising of an oblique post-auricular flap, which is taken from the whole of the middle two-fourths of the pinna, its pedicle lying over the mastoid process, just behind the retro-auricular groove; this flap is later used to line the mastoid segment of the cavity; the mastoid bone is then displayed by a vertical incision, and the posterior wall of the external auditory canal is exposed; a meatal flap, based externally, is cut from the skin of the whole width of the posterior wall of the canal; (3) completion of the tympanoplasty in the usual way; a piece of the split skin graft is used for the reconstruction of the tympanum; (4) covering the raw surfaces with the post-auricular and meatal flaps; (5) closing the fistula, behind the ear, through which the post-auricular flap passes, and covering the defect on the pinna. The dressings are removed on the seventh post-operative day; it will then be found that the skin graft on the pinna has "taken" and the fistula has firmly healed. The method has been used successfully in 25 cases.

Radical mastoidectomy

Technique for primary closure of wound

RAMBO (1958) gives an account of a surgical technique for primary closure of the

wound in radical mastoidectomy. Superior and inferior endaural incisions are made from the drum outwards. The incisions are joined posteriorly by a circumferential incision which is just superficial to the drum. The skin of the posterior part of the external auditory canal is retracted, an elliptical piece of conchal cartilage is removed and the cortex of the mastoid process is exposed. After removal of the diseased tissue the bony posterior wall

after radical mastoidectomy had been performed with the primary closure technique.

Otological grafting

Preserved autogenous skin

WITHERS (1958) describes the use of autogenous skin grafts in the management of

window. Also, the full thickness graft may be employed for closing a residual perforation of the drum. Referring to 30 cases of secondary grafting, Withers comments favourably upon the resistance to intercurrent infection which results from use of the technique. Delayed grafting proved to be successful in 3 cases of facial nerve decompression. Although the decompressed nerve was covered by a tympano-meatal flap facial function was eventually restored

Management of deafness

Scope of surgery

THORBURN (1958) believes that tympanoplasty constitutes the most important development in functional otology since the one-stage fenestration operation was described by Lempert

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week, but the dose varies with the sensitivity of the infecting organism and the

tolerance of the patient. Full-thickness skin grafts provide the medium for reconstructing the new tympanic cavity. Post-aural skin is especially suitable, for it contains relatively few elastic fibres. Usually the new tympanic cavity is filled with absorbent gelatine sponge. The cavity must be in functional continuity with the eustachian tube. Wullstein describes five types of tympanoplasty. In Type I the intact ossicle chain is protected by a bridge of bone and in Type II there may be slight erosion of the ossicles. Type III has reduced leverage, because there is no malleus or incus. For these types the tympanum is closed by means of a skin graft. There is no leverage in Type IV and the stapes is fixed in Type V. Fenestration of the lateral semicircular canal is required for the last type. Mobilization of the stapes is reported to give good results in approximately 35 per cent of cases. One year after the operation a level of 30 decibels, or more, was achieved by Thorburn in 51 of 100 cases and in 85 of a second series of 100 cases.

Chronic suppurative otitis media

Plastic operations

BEALES (1958) discusses the use of plastic operations on the middle ear in the management of chronic suppurative otitis media. Among children and young adults, with adequate cochlear function, if the correct operation is performed a successful result can be obtained even when the degree of sepsis is severe. Improvement is less likely in older patients with nerve deafness, especially when the grafts become sclerotic. If the mastoid requires full exploration and tympanoplasty is not indicated, a full thickness skin graft should be applied to the tympanic cavity. Type I and Type II operations are employed in patients with middle-ear disease if the disease is minimal and the ossicular chain i intact The drum is reflected forwards, the diseased tissue is removed and the dr defect is repaired with a full thickness graft. Care is taken to preserve the sound-co ducting apparatus Gross mastoid disease and interruption of the ossicular chain a indications for Type III and Type IV operations. All diseased tissue is removed unde magnification. The eustachian orifice is separated from the mastoid cavity by a graft. Two-stage operations are applicable in cases of gross sepsis and are of particular value if a relatively large amount of middle-ear mucosa has been removed. Grafts should be thin, and contact with the vascular bed should be adequate. There should be no blood or bone chips beneath the grafts, no sepsis and no excessive trauma when the grafts are cut. In approximately 15 per cent of cases small perforations of the graft appear within a few weeks of the operation, but total loss of the graft is extremely rare. Sometimes a late fall-off in hearing may occur after tympanoplasty. The phenomenon may be associated with failure of the eustachian tube, sclerosis of the graft or cochlear damage. In a series of 142 plastic operations the author used tympanoplasty in approximately 75 per cent of cases and myringoplasty in the remaining cases.

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PROGRESS IN THE CLINICAL USE OF RADIOACTIVE ISOTOPES

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INTRODUCTION

The use of radioactive isotopes was last surveyed in *Surgical Progress* by Dr. E. E. Pochin in 1951 Since then a few applications have found an established place in treatment, a large number of methods has been shown to be of the utmost value in diagnosis and research, and new experimental methods continue to show promise for the future So far medical science does not appear to have been able to take full advantage of the new artificial isotopes now available in abundance This short review can only attempt to be an outline of what has already been tried, concentrating on some of the most recent applications. After a brief guide to the literature, applications in diagnosis and therapy are reviewed in turn, followed by mention of relevant advances in physics and techniques, and finally by a view of the hazards involved in the use of radioisotopes

It is no longer necessary to preface any article on isotopes by a detailed explanation of their nature and production It is as well, however, to recapitulate their basic advantages A radioactive isotope is indistinguishable, chemically or by the body, from stable isotopes of the same chemical element It is different only because it has a different atomic weight and disintegrates or decays at a constant rate, usually expressed in terms of its physical half-life, giving off ionizing radiation in the form of *alpha* particles (very rarely), *beta* particles (electrons or positrons), or *gamma*-rays This ionizing radiation has two properties valuable in medicine: it is capable of extremely sensitive detection and measurement, in the case of *gamma*-rays at a distance, and it can also be used therapeutically with a selective biological action like that of all ionizing radiation

THE LITERATURE

In a hybrid subject such as this it is more difficult than usual to keep up with the literature and a few useful sources are mentioned. First, there are two lists of papers—*Nucle*[illegible]
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bibliography " [illegible]

mainly of British Commonwealth literature. There is a good section on isotopes in the annual *Year Book of Radiology*. As well as the journals of *Radiology*, *Clinical Research*, *Surgery*, and so on, there are two new journals specializing in radioisotopes—the *International Journal of Applied Radiation and Isotopes* and *Nuclear Medizin*. There are now several regular relevant conferences—the "United Nations Conference on the Peaceful Uses of Atomic Energy", held in 1955 and 1958 at Geneva, the U N E S.C.O. conference on "Radioisotopes in Scientific Research", held at Paris in 1957, and several smaller but useful meetings, such as the biennial conference "Radioaktive Isotope in Klinik und Forschung", held at Bad Gastein in 1954, 1956 and 1958, and the "Annual Meeting of the American Society of Nuclear Medicine" All of those have published proceedings.

Among the best of the recent books have been those of Beierwaltes, Johnson and Solari (1957) and of Hahn (1956) on therapeutic uses, and of Veall and Vetter (1958) on diagnostic applications Other recent American texts include those by Blahd, Bauer and Cassen (1958) and by Quimby, Feitelberg and Silver (1958), and one edited by Claus (1958). The literature is now vast. From 1955 to 1957 inclusive over 1,000 papers on medical applications of radioisotopes were published in the North American journals alone. References given here are mainly to the most recent useful papers and to a few key earlier articles, particularly to those published in English. The abstracts following this article have been chosen as a representative sample of those published in 1958, and include new and unorthodox views as well as reports on established and standard techniques.

DIAGNOSTIC APPLICATIONS

Diagnosis and clinical research is still the field in which radioisotopes have proved most useful.

There are now many methods of measuring the metabolism and function of different organs or systems, particularly of the thyroid gland, of haematopoiesis, and of the liver, the kidneys, the lungs and the bones

The thyroid gland

The most usual diagnostic method employing radioisotopes is still the use of radio-iodine in the investigation of the thyroid gland, for which there are many different methods available. Recent papers have shown the usefulness in the diagnosis of thyroid over-activity of early uptake tests (often at 2 hours) after an oral dose of radio-iodine Measurement at about this time takes advantage of the quicker speed of uptake of the hyperthyroid gland as well as of its higher maximum uptake Realization that whatever test is used there will still remain "borderline" results not giving a clear result has led to the wider use of additional refinements. The diagnosis of hyperthyroidism can often be confirmed by the fact that administration of dried thyroid, thyroxine, tri-iodothyronine or iodine will cause reduction of the radio-iodine uptake of normal glands or of non-toxic goitres but not of toxic goitres. Primary hypothyroidism and hypothyroidism secondary to hypopituitarism can sometimes be more clearly identified by the study of radio-iodine uptake before and after the injection of pituitary thyrotropic hormone (Fletcher and

Besford, 1958; Skillern and Evans, 1957). The short-lived iodine-132 (half-life 2·3 hours) is coming into wide use especially now that a simpler method of preparation from tellurium-132 is under trial (Stang and his colleagues, 1957) ^{132}I has the advantages of giving a much reduced radiation dosage to the patient, particularly necessary in tests on children and the occasional pregnant patient, and of enabling tests to be repeated at short intervals.

The blood

The second large group of radioisotope tests is that relating to the formation and properties of the blood.

Vitamin B_{12} labelled with radiocobalt can be administered, with and without intrinsic factor, and its absorption estimated by measurement of radioactivity in faeces or in urine, or by its uptake in the liver. This can help in the diagnosis of pernicious anaemia—even after treatment with liver extract—and of the macrocytic anaemias associated with steatorrhoea and poor intestinal absorption, or after gastrectomy. Iron-59 can be used to investigate the production and destruction of red blood cells. One can measure iron absorption, plasma iron turnover, and red cell iron turnover. Alternatively, it is possible to make *in vivo* measurements of the whole body and to gain some idea of the distribution of active haematopoietic tissue; this can also be done with radioactive gold-198 The life-span of all the different blood cells can now be measured ^{32}P was first used, but more recently chromium-51, which has a convenient *gamma* emission, has come into wide use. *In vivo* measurements can then also be made to determine the sites of red cell destruction It has been suggested that this method might be of great value in deciding whether an enlarged spleen is the site of abnormal haemolysis and splenectomy therefore of value, or the site of abnormal haematopoiesis and splenectomy potentially disastrous Very recently it has been claimed that a far more reliable label is DFP^{32} (di-isopropylfluorophosphate), and it has been found possible to label platelets and white blood cells as well as red.

Liver function and blood flow

Liver function and physiology are now routinely investigated. Colloidal particles of a given size are removed from the blood by the liver and the blood flow through it can therefore be calculated, using colloidal chromic phosphate, denatured albumin labelled with ^{131}I, or colloidal gold Liver function may be measured more directly by administering ^{131}I-labelled rose bengal, and measuring the rise of radioactivity in the liver as the dye accumulates there and the subsequent fall as it is excreted in the bile It is often possible to obtain help in this way in the differential diagnosis of jaundice, and to find out whether obstruction is present

Renal function and plasma flow

Renal function may also be estimated by a similar method using ^{131}I labelled diodrast (Taplin and his colleagues, 1958). Separate collimated scintillation counters can be used over each kidney and the concentration and excretion through both seen. If urine and blood samples are taken the renal plasma flow can also be estimated accurately (Schlungbaum and Billion, 1956).

Skeletal metabolism

Calcium metabolism in human bone has not yet been studied in detail by isotope techniques because of the undesirably long half-life (160 days) of the most easily obtainable radiocalcium—^{45}Ca. Recently, it has become a little easier to obtain ^{47}Ca, which has a half-life of only 5 days, and some useful work with this has already been reported [illegible] has also [illegible] *isotopes* are easily available, and because of the importance of ^{90}Sr in relation to nuclear explosion fall-out absorption in man.

Lung function

Lung function is not easy to estimate by radioisotope methods because of the facts that carbon-14 has a very long half-life, oxygen-15 very short, and that no radioisotopes of nitrogen are known. ^{15}O has a half-life of only 2 minutes but some very elegant pioneer work has recently been reported from Hammersmith Hospital where it was used to investigate human pulmonary function (Dyson and his colleagues, 1958). The radio-oxygen was prepared there using a cyclotron, and advantage was also taken of the positron emission, so that coincidence counting techniques could be used as in brain tumour scanning (*see* below).

Cardiac output, blood flow and blood volume measurement

"Radiocardiography" and blood flow measurements are now usual. No new advances have been reported in the very useful radioisotope methods used to demonstrate development or failure of circulation in plastic and orthopaedic surgery. Recent advances include the use of methyl radio-iodide and radiokrypton (Jaimet and his colleagues, 1958), and the measurement of cerebral blood flow (Crandall and Cassen, 1958). Blood volume was one of the earliest parameters measured by radioisotopes. ^{51}Cr or ^{131}I or ^{132}I labelled serum albumin can now be used instead of ^{32}P, and relatively early rough estimates may be obtained, useful in the management of surgical patients A useful later development is the extension of this method to measurement and detection of blood loss, particularly occult loss in faeces.

Gastro-enterology and obstetrics

Radioisotopes have also entered the fields of gastro-enterology and of obstetrics. Gastric secretion and emptying have been measured with ^{95}Zr-Ni, and fat absorption and pancreatic function measured using ^{131}I-labelled fat, and proteins. In obstetrics research continues on uterine blood flow measurements and on sodium and potassium metabolism, particularly in relation to pre-eclampsia. Methods of placental localization are also being improved.

Electrolytes and recent advances

The distribution and concentration of many different ions present in the body have now been measured in terms of the appropriate radioisotope, including sodium, potassium, magnesium, calcium, copper, molybdenum, zinc, phosphate,

sulphate and chloride. Other diagnostic methods of interest include the use in pharmacology of radioisotope labelled drugs, such as insulin and cortisone, and of activation analysis. This last method uses the advantage of extreme sensitivity of radioisotope measurement without the necessity of administering a radioisotope to the patient The tissue or blood sample to be analysed is made active by neutron bombardment in a reactor. The different isotopes produced can then be separately analysed because of the different energies emitted, and their different half-lives. The arsenic content of hair can be determined in this way with great sensitivity, as also can many blood electrolytes. One further technical advance must be mentioned· hydrogen-3, tritium, is now available and its use should lead to important advances in research on fundamental intracellular metabolism, since its very low *beta* energy implies that autoradiographs can be made with much finer definition and precision than has hitherto been possible (Hughes, 1958).

Tumour detection

Tumour detection and localization has always been of great interest potentially, but practically useful methods have been few All methods rely on an increased uptake, of the isotope being used, in tumour relative to normal tissue at a particular time. The oldest method—using ^{32}P—seems of some clinical value in two particular regions—in detection of intra-ocular malignancy and in confirmation of the diagnosis of malignant melanoma in the skin Decision on removal of an eye or on wide mutilating excision of a malignant melanoma needs every possible preliminary aid and the use of ^{32}P can often be of considerable help when biopsy is difficult or undesirable.

Localization and detection of intracerebral tumours is also extremely difficult. Technical difficulties are still considerable and the simple brain scan after administration of ^{131}I-labelled di-iodofluorescein or serum albumin is only of slight help Measurement of ^{32}P uptake by needle counter is of some value but can obviously only be done at craniotomy and not before Use of positron emitting isotopes would seem to repay further study (Brownell and Sweet, 1956) A positron penetrates only a very short distance in tissue before it is "annihilated" by combination with an electron, invariably resulting in the emission of two *gamma*-rays in opposite directions If two scintillation counters are placed on either side of the patient's head a "coincidence" circuit can be arranged so that only rays received simultaneously by the two counters are recorded. Nearly all background radiation will be eliminated by this means, and the very slight differences in uptake between tumour and normal brain tissue can be detected and localized more easily Useful work with this method has already been reported, using arsenic-74.

THERAPY

Therapeutic uses of radioisotopes do not at first glance seem so many or so valuable as do their applications to diagnosis and research. This is partly because radiotherapy using the pioneer radioisotope, radium and x-rays had already been so well developed Some of the most effective radioisotope therapeutic techniques are,

therefore, the replacement and sometimes improvement of the accepted methods of x-ray treatment by radiocobalt or radiocaesium teletherapy units, and of interstitial, intracavitary and "mould" radium or radon treatment, by radiocobalt, gold, iridium and other isotopes (Figs. 85–87). The few methods of treatment by intravenous or oral administration of radioisotopes are reviewed first.



(*a*)



(*b*)

... of the neck

Metabolic methods

Oral or intravenous systemic administration of radioisotopes is still almost confined to the two common elements iodine and phosphorus.

Radio-iodine treatment of thyroid disease

Treatment of thyroid disease by radio-iodine continues. Treatment of thyrotoxicosis by ^{131}I is now widely accepted. Empirical methods of dose selection are



(*a*)

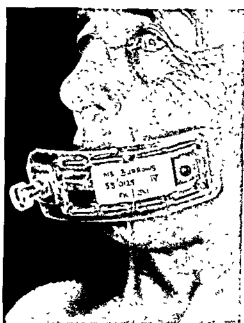
FIG. 86.—(*a*) A very extensive carcinoma of the skin spreading over the temple, cheek and outer canthus treated by (*b*) a cobalt-60 mould. (By courtesy of Dr. Ralston Paterson and his colleagues.)



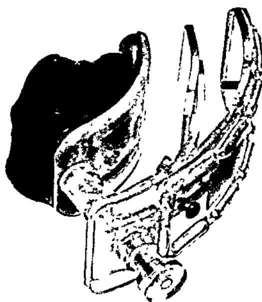
(*b*)



(*a*)



(*b*)



(*c*)

becoming more common. No radiotherapist will claim better results than are obtained by good surgery in a properly prepared young patient, previously untreated, therefore it still seems wise to restrict radio-iodine treatment in patients under an arbitrary age of about 45 years to those in whom antithyroid drugs and surgery are unsatisfactory or relatively unsafe. Thus the younger patients for whom radio-iodine is selected are mainly those with hyperthyroidism recurrent after previous surgery and those who are too ill for safe thyroidectomy. It now seems undeniable that the infant or child's thyroid gland is particularly liable to carcinogenesis after external irradiation, and it is undesirable to use radio-iodine at all in children, except for tests with ^{132}I when essential. However, this does not appear to apply to the adult thyroid—indeed x-ray treatment of thyrotoxicosis has led to an increased rate of skin cancer, sarcoma and carcinoma of the hypopharynx but not of thyroid cancer. There is the additional possibility of leukaemogenesis after radio-iodine, though no increased incidence has yet appeared after treatment of thyrotoxicosis, but only after treatment of thyroid carcinoma with very high dosage of radio-iodine If leukaemogenesis does become a serious hazard the use of iodine-133 has been suggested so as to give relatively lower plasma radiation (Berman, Becker and Benua, 1957).

Radio-iodine continues to play a part in the treatment of thyroid cancer, and the importance of thyroid ablation and of repeated adequate treatment has been stressed. Iodine-124 may be useful because of its high energy emission, if only it can be produced in sufficient quantity, from a cyclotron The importance of supplementary treatment with thyroid hormone is becoming widely recognized

Radio-iodine induction of partial hypothyroidism in patients with advanced cardiac disease also continues to be used with benefit if cases are correctly selected; anginal pain is the symptom most often relieved, a dose of ^{131}I of about 15–25 millicuries being given.

Radiophosphorus treatment

Treatment of leukaemia and polycythaemia by phosphorus-32 is now also well established Empirical methods of dose selection are usually used, but Osgood, Seaman and Tivey (1955) continue to claim good results for their method of "spaced titrated" administration A more attractive method appears to be that of Easson, Jones and Mackenzie (1955), by which a minimum correct dose can be

with less certain benefits from chemotherapy using pyrimethamine or thioTEPA.

Phosphorus-32 is used from time to time in other classes of malignant disease but does not seem of great value Interest was awakened at the Seventh International Cancer Congress to the surprisingly high proportion of patients with malignant disease in whom cancer cells may be found in the blood, even in early stage 1 cases, and it has been suggested that nitrogen mustard or other chemical should be given at the time of operation, when relatively large showers of cells can be demonstrated in the blood This revives the alternative possibility of

giving ^{32}P at the time of a radical mastectomy or other operation as was practised by Low-Beer many years ago, and has recently again been reported (Bell and Low-Beer, 1955).

Radioactive antibodies

Research has been proceeding for several years on preparation of a labelled molecule that will be localized and concentrated specifically in a cancer cell. One approach is the use of immunological techniques to prepare radioactive antibodies, and considerable experimental animal work has already been done. Similar attempts are being made at labelling compounds, such as Synkavit, which are concentrated in malignant cells.

Interstitial use of radioisotopes

Implantation of radium needles and of gold seeds containing radon can be replaced by use of radioisotopes, but there is no clear evidence that better treatment can be given in some sites, such as the mouth, where radium or radon are particularly suitable. Cobalt-60 needles, gold-198 "grains" and tantalum wire "hairpins" are, however, of value in carcinoma of the bladder—where it is very difficult to use radium needles, and not easy to perform a reasonably good radon seed implant, whereas the flexible tantalum hairpins can often be made to form quite good implants. The Royal Marsden Hospital gold grain "gun" is now in widespread use for treatment in many parts of the body, and is claimed to give more accurate implants than those with radon seeds because a magazine is used and the introducer does not have to be repeatedly withdrawn and reinserted.

Less orthodox methods have mainly been tried abroad. Interstitial injection of colloidal gold-198 and other isotopes has not found much favour in Great Britain because of the impossibility of achieving a homogeneous distribution of activity, the liability of the colloid to leave the tumour bed by blood and lymph channels and arrive in the liver, spleen and bone marrow, and the theoretical possibility of the pressure of the injection disseminating tumour cells into the general circulation. Nevertheless two applications at least deserve examination—injection of inoperable prostatic cancer and injection of the parametria in the presence of cancer of the uterine cervix, since long-term results are now appearing.

Prostatic cancer

Radiogold treatment of prostatic cancer has been used at Iowa since 1951. Colloidal gold is injected retropubically (from the opened bladder), through the perineum, or (rarely) transrectally. Other workers have used a similar technique employing radioactive chromic phosphate. The originators of the technique are still using it, and have recently published their latest results (Elkins, Flocks and Culp, 1958)

Rectal ulceration was a serious complication initially but appears almost to have been eliminated by improvement in technique. The 5-year survival of 134 patients is only 34 per cent, although including many patients with advanced disease. It is interesting to note that of 11 patients with a gland initially estimated

to weigh under 20 grammes, 10 are alive, 9 without evidence of disease. It is admitted that a substantial proportion of the injected gold may enter the blood stream, but there has been no case of death from aplastic anaemia. Perhaps the technique has not been more widely adopted because of the already difficult decision as to treatment plan from prostatectomy by many methods, orchidectomy, oestrogen administration, adrenalectomy and hypophysectomy

Cancer of the cervix uteri

Gold-198 treatment of cancer of the cervix is an attempt to irradiate not the primary cancer but secondarily involved pelvic lymph nodes This treatment also has a long history, having been used at Washington University, St. Louis, since 1950 (Allen, Sherman and Camel, 1958) and has been used in a few other hospitals, particularly the Radiumhemmet in Stockholm (Kottmeier and Moberger, 1955). Two weeks after conventional radium treatment, 50–70 millicuries of colloidal gold-198 are injected transvaginally into each parametrium It is claimed that the gold is "picked up by the lymphatics and filtered out by the pelvic lymph nodes" The gold injection is used as an alternative (claimed to be superior) to supplementary external irradiation It is not clear how patients are selected but the results as quoted undoubtedly appear good, with an overall survival rate at 3–7 years of 80 per cent, including 54 per cent of 24 stage 3 cases and 74 per cent of 58 stage 2 cases.

Treatment of lymph nodes

It should be mentioned here that there have now been very many demonstrations in man and animals that it is not justified to assume that a lymph node containing any substantial quantity of carcinoma will retain radioactive or other particles in the same way as a normal healthy node. Whatever particles are used the same disappointing result seems to occur, namely, collection of particles in many different lymph nodes except where there are already deposits of cancer. However, it is possible that such relatively large radiation doses are given to the lymph nodes in the parametrial injections just referred to that even heavily invaded nodes received some effective radiation, as well as those with only a few or no malignant cells. Hahn is still trying the effect of silver-coated colloids (Matuska and his colleagues, 1958).

Other cancers

Attempts at interstitial treatment of many other difficult types of cancer are still being made—notably with iridium-192 and gold-198 to lung cancer and various isotopes inserted into the internal mammary vessels to treat lymph nodes metastatically invaded by breast cancer (Brasfield and Henschke, 1958). Harper's method of using ^{131}I in polythene tubing is also interesting (Harper and his colleagues, 1956).

One new approach is the use of pure *beta* emitters, such as yttrium-90 There do seem to be potential advantages here, particularly in the relatively strict limitation of the radiation emitted, and it may be worth considering the use of ^{90}Y in

sites other than the pituitary, for example, in nodes just under skin already irradiated and in the brain not only for malignant disease but also for Parkinsonism and similar disorders.

Radiation hypophysectomy

This technique is one of the most interesting of current interstitial uses of radioactive isotopes This article is not the place to discuss the merits of hypophysectomy as against adrenalectomy and oophorectomy. There has been a well argued discussion of the problem published in book form (Currie, 1958). At present it appears justifiable to accept the premise that hypophysectomy can give a temporary remission in about half of all cases of metastatic breast cancer, or can give as good results as can be achieved by adrenalectomy and oophorectomy.

Surgical hypophysectomy is clearly a major operation with its own risks. Thus Luft and his colleagues (1958) had 4 operative deaths and 3 deaths from post-operative complications in 59 operations; Ray and Pearson (1958) reported an immediate mortality of 3 per cent and total post-operative mortality of 7 per cent. The alternative simpler operation of stalk section is being tried but may not produce as adequate and consistent pituitary necrosis.

Radiation hypophysectomy has its problems too. External radiotherapy using beam directed x-rays has been used for many years to treat relatively radiosensitive pituitary tumours but is not adequate, with conventional methods, for destruction of the normal pituitary, even when radiation doses as high as 10,000r. are used. Lawrence, Tobias and Born (1958) have demonstrated that pituitary ablation can be achieved by a dose of 30,000 rads in 2 weeks, using 340 mega-electronvolt protons from a large synchrocyclotron. This technique, although apparently first class, cannot at present be repeated at more than two or three centres throughout the world. Radioactive isotope sources are, however, widely available. Radon gold seeds or radioactive gold-198 grains have first been tried since there is so much clinical experience with them in other sites. Radon seeds were used initially in Glasgow but there was serious loss of vision in 7 of 45 patients, suspected to be caused by damage to the optic chiasma (Forrest and his colleagues, 1956). Gold seeds have been used at the Royal Marsden Hospital and at Oxford and are still being used at Heidelberg, apparently without serious visual complications.

The radiation from radon seeds is composed of *gamma*-rays which therefore give a radiation dosage which only decreases in intensity gradually with distance. *Beta*-rays, however, behave quite differently, with a strictly limited range dependent on their energy Theoretically, therefore, an isotope emitting *only beta*-rays might be expected to be more useful in giving high dosage to the pituitary itself while avoiding adjacent structures Two isotopes of this kind have been used, phosphorus-32 and yttrium-90. Radiophosphorus has been used in the form of colloidal chromic phosphate. However, this method does not seem of great value as tried so far; it is probable that the radioactive phosphorus in this form does not stay in the sella turcica.

The use of yttrium-90 was first well tried in monkeys and is now in extensive use in many centres with some results already available (Currie, 1958; Moseley,

Ironside and Harper, 1958). Pathological investigations suggest that a high radiation dosage (of 70,000 rads or more) is needed for consistent necrosis but this can be obtained.

Techniques for ^{90}Y implantation vary. A drill, needle, or trochar and cannula, is inserted through the nostril directly into the sphenoidal sinus and then into the

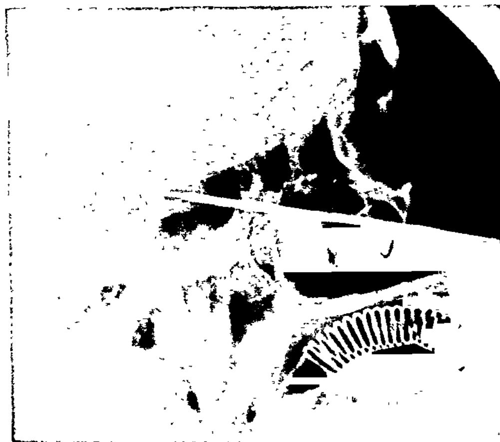


FIG 88 —Lateral radiograph of the skull, taken by image intensifier, demonstrating implantation of the pituitary gland with ^{90}Y pellet passed thro[illegible]

sella turcica (Fig 88). If intermittent radiographs only can be taken, some kind of jig, guide, or "stereotaxic" system is used With an image intensifier the insertion can be made under direct fluoroscopic control and it then becomes possible to do the whole procedure free-hand under a local anaesthetic. Harper inserts six to eleven 1 5 millicurie pellets, Forrest two 6–7 millicurie rods. Possible complications include visual field defects or cranial nerve palsies owing to incorrect position of yttrium

sources, and cerebrospinal rhinorrhoea. This last persistent complication can be common, occurring in as many as 25 per cent of patients, and is probably due to poor healing of the holes made in the sella turcica in the presence of intense local radiation. It is possible to insert agar or other plugs and Forrest, Blair and Valentine (1958) were attempting to leave a permanent threaded metal plug *in situ*.

Preliminary results suggest that results can be obtained which are comparable with those after surgical hypophysectomy and those after adrenalectomy and oophorectomy. It may finally be mentioned that it is possible to combine both methods of hypophysectomy, and that a trial is in progress in Belfast (Edelstyn and his colleagues, 1958) of surgical hypophysectomy followed by packing the sella turcica with a wax paste containing powdered yttrium-90, similar to Radley-Smith's (1957) earlier method of post-operative packing with fibrin foam containing radioactive gold.

This discussion has been in relation to advanced carcinoma of breast and prostate but if radiation hypophysectomy becomes a standard procedure it might also be valuable in advanced cases of thyroid and other cancer, and perhaps even in advanced diabetes mellitus, malignant exophthalmos and pituitary tumours

Intracavitary treatment

Malignant effusions and ovarian cancer

Instillation of colloidal gold-198 has now been widely adopted for palliative treatment of mal[illegible] Most reports agree that this *treatment* can stop or slow [illegible] untreated masses [illegible] It is, however, still uncertain that equally good results cannot be obtained by instillation of chemicals such as nitrogen mustard or thioTEPA. The prophylactic use of colloidal radiogold in treatment of ovarian carcinoma is of less certain value but Muller (1958) has now reported results of a treatment policy consisting of surgery, colloidal gold and external irradiation; his results appear better than any previously reported. Use of a pure *beta* emitter instead of radiogold is of possible value and chromic phosphate and yttrium are under trial.

Endometrial disease

Beta emitters are also of value in the treatment of premenopausal endometrial abnormalities when it is desirable to limit ovarian radiation, and strontium-90 can be used.

Bladder cancer

Instillation of colloidal gold direct, or of radiobromine solution in a balloon, in the urinary bladder for treating superficial carcinoma has been under trial for some years (Hahn, 1956), but it is still claimed that the older method of using a central radium or radiocobalt source will give a better depth dose and may be used for more infiltrating lesions. Becker and Scheer (1958) continue to use radiocobalt in a "makrosuspension" and as threaded "pearls" in the treatment of carcinoma of the bladder and uterus as well as of other sites.

Radioisotopes in ophthalmology and dermatology

Many benign and malignant diseases of the skin and eye can be well treated by *beta*-rays from strontium-90, phosphorus-32, or cerium-144

Telecurie therapy

Cobalt-60

Teletherapy—use of radioactive sources at a distance from the patient of 10–100 centimetres in a container specially designed so that an adjustable and controllable beam of *gamma*-rays is emitted—is at present the most valuable therapeutic use of radioactive isotopes. Progress in this field has been very rapid and is now increasing exponentially.

Radium had been used in this way for many years, but the scarcity and expense made it impossible to use larger quantities usually than about 10 grammes or curies. This meant that the intensity of the beam of *gamma*-rays was very low, and long treatment times and short source-skin distances had to be used. The availability of radioactive isotopes has allowed the use of sources of over 100 times this activity Thus, teletherapy units can now be constructed with the same output intensity and flexibility as conventional x-ray treatment units, and with a further advantage If the isotope used emits *gamma*-rays of high energy, these can be comparable to or better than the "megavoltage" x-ray generators, such as the Van de Graaf unit and linear accelerator, which produce x-rays of over 1 million electronvolt energy.

The technical advantages of megavoltage therapy, that are attainable by use of teletherapy cobalt-60 units, have recently been summarized by Paterson (1958). It is important to make the preliminary point that there is not any inherent biological superiority of high-energy radiation over the conventional x-rays (from 200 to 500-kilovolt machines) that have been used so widely In fact one of the facts now clearly established by many different clinical and radiobiological experiments has been that there is a lower "relative biological efficiency" (R.B.E.) at the higher energies, for example, the R.B E of the x-rays from a 4-megavolt linear accelerator is about 85 per cent compared with conventional 300-kilovolt x-rays This is, of course, neither an advantage nor a disadvantage, but essential preliminary knowledge to comparison of the therapeutic effects of different energy x-rays or *gamma*-rays

The first essential advantage of megavoltage radiation is that the point of highest energy absorption is below the surface of the skin (about 6 millimetres below for ^{60}Co radiation) This means that the skin reaction, which often needs to be severe when treatment is given by conventional medium energy x-rays, can be considerably lessened, providing the skin is not infiltrated by tumour To take advantage of this, treatment fields have to be "open", without solid applicators or wax over the skin

The second advantage is that the radiation is of high penetration, so that it becomes very much easier to deliver adequate radiation to deep-seated tumours of, for example, the lung, oesophagus and urinary bladder. Thirdly, there is very little difference in absorption of megavoltage radiation in tissues of different density such as bone and lung (whereas lower energy radiation gives a higher

sources, and cerebrospinal rhinorrhoea. This last persistent complication can be common, occurring in as many as 25 per cent of patients, and is probably due to poor healing of the holes made in the sella turcica in the presence of intense local radiation. It is possible to insert agar or other plugs and Forrest, Blair and Valentine (1958) were attempting to leave a permanent threaded metal plug *in situ*.

Preliminary results suggest that results can be obtained which are comparable with those after surgical hypophysectomy and those after adrenalectomy and oophorectomy. It may finally be mentioned that it is possible to combine both methods of hypophysectomy, and that a trial is in progress in Belfast (Edelstyn and his colleagues, 1958) of surgical hypophysectomy followed by packing the sella turcica with a wax paste containing powdered yttrium-90, similar to Radley-Smith's (1957) earlier method of post-operative packing with fibrin foam containing radioactive gold.

This discussion has been in relation to advanced carcinoma of breast and prostate but if radiation hypophysectomy becomes a standard procedure it might also be valuable in advanced cases of thyroid and other cancer, and perhaps even in advanced diabetes mellitus, malignant exophthalmos and pituitary tumours.

Intracavitary treatment

Malignant effusions and ovarian cancer

Instillation of colloidal gold-198 has now been widely adopted for palliative treatment of malignant ascites or effusion. Most reports agree that this treatment can stop or slow down formation of fluid in over half of all patients without large untreated masses of carcinoma who are in reasonably good gener[illegible]n. It is, however, still uncertain that equally good [illegible]y instillation of chemicals such as nit[illegible]; use of colloidal rad[illegible]. but Muller [illegible]g of surgery, coll[illegible]s appear better than any previously re[illegible] emitter instead of radiogold is of possible value and chr[illegible]phate and yttrium are under trial.

Endometrial disease

Beta emitters are also of value in the treatment of premenopausal endometrial abnormalities when it is desirable to limit ovarian radiation, and strontium-90 can be used.

Bladder cancer

Instillation of colloidal gold direct, or of radiobromine solution in a balloon, in the urinary bladder for treating superficial carcinoma has been under trial for some years (Hahn, 1956), but it is still claimed that the older method of using a central radium or radiocobalt source will give a better depth dose and may be used for more infiltrating lesions. Becker and Scheer (1958) continue to use radiocobalt in a "makrosuspension" and as threaded "pearls" in the treatment of carcinoma of the bladder and uterus as well as of other sites.

Radioisotopes in ophthalmology and dermatology

Many benign and malignant diseases of the skin and eye can be well treated by *beta*-rays from strontium-90, phosphorus-32, or cerium-144

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Cobalt-60

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dosage to bone and a lower absorption in lung than in other tissue). This me
that it is less difficult to give the correct dosage to a tumour inside the skull
pelvis, and that late bone necrosis, as has sometimes occurred in the jaw, r
and femur, will also be less likely and need not limit treatment planning.

The fourth advantage is an extremely useful technical point: treatment fiel
can with ease be made oblique by a wedge filter, so that relatively superficial region
such as the maxillary antrum, the anterior mediastinum or the middle ear can also
be treated better, with less unnecessary radiation of deeper structures.

Megavoltage radiation when correctly used can thus lead to more effective
treatment of malignant disease in many sites, often with less severe symptoms to
be experienced by the patient.

These potential advantages have been appreciated all over the world in the case
of cobalt-60. There are now over 300 teletherapy units already using sources
supplied from North America. It is still too soon to evaluate results achieved with
them, but it has been common to read that better results in terms of cure rate will
not be experienced, better palliation being the main achievement. There was
discussion on this point at the 1958 Geneva Conference and it was noteworthy
that Paterson did not agree and expected improved cure rates in those fields in
which cure rates were already high, such as tumours of the mouth and larynx, as
well as in deep-seated tumours such as those of the bladder. Randomly controlled
trials contrasting conventional and megavoltage treatment are proceeding at
Manchester which should give an irrefutable answer in 3 or 4 years' time.

Meanwhile some results have already been reported. One of the first large
cobalt units was installed at London, Ontario, Canada, and some early results
on small numbers are very encouraging (Smith and his colleagues, 1958; Smith
and Lott, 1958) For instance, in carcinoma of the mouth 3 out of 4 patients with
tumour invasion of the mandible are alive and well after 34, 61 and 64 months, and
in intrinsic carcinoma of the larynx 11 out of 13 patients are alive without disease
at from 31 months to 6 years. In a less favourable site, the oesophagus, there were
7 long-term survivors out of 31 patients given radical treatment for carcinoma.

Caesium-137

There have also been many papers recently suggesting that caesium-137 may be
useful (Brucer and Simon, 1958) It may be unfair to suggest that the Atomic
Energy Authorities, on both sides of the Atlantic, are only too grateful to be able
to sell a fission-product (which their reactors are inevitably producing in large
quantities), rather than cobalt-60, which has to be produced in very high neutron
flux reactors which are also in great demand for other purposes. The only advant-
ages that caesium-137 possesses over cobalt-60 are economic; it has a longer half-
life (30 years instead of 5¼) and a lower energy *gamma*-emission, 660 keV compared
with 1·1 or 1·3 mega-electrovolt. Radiocaesium, therefore, needs replacement less
often and units using it can be constructed with much less efficient, and therefore
cheaper, shielding However, there are disadvantages. First, it is very much more
difficult to prepare sources as small as those of ^{60}Co with a similar intensity of
gamma radiation, and secondly the lower energy *gamma*-rays will inevitably have
a poorer penetration and less skin sparing effect than those from cobalt-60 It

should not be denied that more patients can be treated more effectively with a kilocurie cobalt-60 unit than with the best caesium-137 unit so far constructed

Nevertheless several useful caesium units are now coming into use. Physical measurements on these suggest that they may give better results than conventional x-ray units although not able to compete in output or penetration with large cobalt-60 machines.

Neutron-capture therapy

This method of treatment is still highly experimental, and requires a nuclear reactor; its use is thus unlikely to be widespread in the immediate future. However, the principles involved are novel and interesting, and the theoretical possibilities are certainly good

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gliomas has not been conspicuously successful, as is being made particularly clear by controlled trials, such as that at the Royal Marsden Hospital, London. Gliomas are ill defined physically and difficult to localize, and their radiosensitivity appears to be close to that of normal cerebral tissue. However, there seems no doubt that the normal "blood-brain barrier" is broken down in areas of tumour (and some other abnormalities) and that some compounds injected intravenously will reach higher concentrations in brain tumour than in normal brain, especially at a certain period after injection. It has not proved possible to concentrate a radioactive isotope in brain tumours in concentrations suitable for treatment (although enough for diagnosis, as already mentioned), but it is possible to achieve a good concentration of certain stable isotopes, especially boron Now when boron-10 is exposed to a beam of low-energy "thermal" neutrons, "capture" of neutrons occurs with a reaction resulting in production of ionizing particles of very short range. The thermal neutron beam itself has little biological action, so that there will be effective, very localized radiation only where boron-10 is concentrated, that is, in the brain tumour This possibility was first suggested in 1952 and was followed by a cautious trial on a few patients with glioblastoma multiforme, using the reactor at the Brookhaven National Laboratory in the United States. There have been many technical difficulties, particularly insufficient penetration by available neutron beams and unexpected skin reactions Less than 30 patients have been treated so far but the results are sufficiently promising to continue the trial with improved techniques A second trial is also about to take place in the United States using

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concerned.

PHYSICS AND TECHNIQUES

Mention should first be made of the new list of isotopes published in 1958, over

twice as long as the previous one, and an invaluable source of reference (Strominger, Hollander and Seaborg, 1958); and of a recent paper giving more accurate values for mean *beta* energies than were previously known (Loevinger, 1957). There is also a very good section on radioisotope dosimetry in Hine and Brownell (1956).

Counting methods continue to improve. Scintillation counting methods are being improved by better and larger phosphors, and also by pulse height selection—a method of eliminating all pulses except for those of the energy desired, emitted by the isotope being counted. Scattered radiation is mostly of lower energy and can therefore also be eliminated, together with much undesired background radiation.

Scanning methods

Scanning methods still seem to be advancing. A good realization of conventional methods has been developed at Stockholm resulting in a practical arrangement which will provide both good two-dimensional "scintiscans", and quantitative "profiles", as required (Jonsson, Larsson and Ragnhult, 1957). Photographic and electronic techniques are being used to provide "pictures" with better contrast and less background (Bender, 1957). A pinhole scintillation camera has also been described (Anger, 1958). The very latest technique is to make scanning pictures in colour (Mallard, 1959).

Whole body counters

Whole body counters have also been developed: simple arrangements with a few Geiger or scintillation counters of great practical value in electrolyte measurements and very complex, highly sensitive counters to measure natural and absorbed body radioactivity.

Isotope radiography

Isotope sources of practical use in diagnostic radiology are still not available, though the use of europium-155 and promethium-147 has been added to that of thulium-170 and xenon-133.

Medical reactors and cyclotrons

It has been seriously suggested that medical use of nuclear reactors should be contemplated (Libby, 1958). Two categories are suggested—the large reactor which can provide neutron beams suitable for treating patients (possibly with neutron-capture therapy, as described above), and smaller reactors which could provide short-lived isotopes in the hospital where they are needed. Short-life isotopes can be of use in diagnosis and research, first because of the much lower radiation exposure of the patient being investigated, and secondly because the only radioactive isotopes known of some elements, such as oxygen and fluorine, are short-lived. Thus iodine-132 (half-life 2.3 hours) is already in wide use and it is now suggested that iodine-128 (half-life 25 minutes) might be used instead. An alternative useful source of short-life isotopes is a cyclic accelerator, such as the cyclotron, which can produce very useful isotopes, such as oxygen-15, iron-52 and iodine-124.

HAZARDS OF RADIATION

No review of the clinical use of radioactive isotopes would be complete in 1959 without some mention of the hazards of radiation. The Report of the United Nations Scientific Committee (1958) gave a full and valuable review of nearly all that is at present known on this subject, though its final conclusions did not differ significantly from those of the earlier report from the British Medical Research Council (1956).

The important hazards in general are those of genetic damage to the population as a whole, in the future, and of the hazard to an individual of induction of malignant disease after a latent period usually of many years. It is important to distinguish between these two because they pose quite different problems.

Genetic hazard

The genetic hazard is only very poorly delineated. Its assessment depends almost entirely on a vast body of knowledge accumulated from experiments on Drosophila, the fruit fly (and on plants); and a few experiments using hundreds of thousands of mice, all extrapolated to man. It seems reasonable to accept that all ionizing radiation, in however small doses, causes irreversible, strictly cumulative genetic mutation This genetic mutation is usually both harmful and recessive, incapable of revealing itself except in later generations. Genetic damage of this kind can, therefore, only be of significance if it occurs before reproduction Mutations of this kind are already occurring spontaneously (and are the means by which natural selection and evolution can take place) and the radiation hazard is usually expressed in terms of the quantity of radiation—about 50r —that will double the spontaneous mutation rate. What changes of this kind would mean to the human race is not at all clearly known, but it is probable that there would be an increase in mental disease and of many other organic diseases, such as diabetes mellitus, in which there is a genetic component (Carter, 1957). However, because of the recessive nature of genetic damage, and its random allocation, harm can only ensue if very large numbers of young patients are exposed to radiation; and it appears largely irrelevant when one is deciding on the merits, say, of ^{131}I and of surgery for treating an *individual* young thyrotoxic patient. The latest calculations suggest that the present or immediate future use of radioactive isotopes can only contribute a small proportion of genetic damage, in comparison with the far more widespread radiation from diagnostic radiology.

Induction of malignant disease

Induction of malignant disease appears of much more importance in this context It has been well known for years that severe radiation damage to tissue can cause later skin cancer, sarcoma, or post-cricoid carcinoma of the hypopharynx. It is also known that ingestion of radium can lead to bone sarcoma and that inhalation of radon, as in radioactive mines at Joachimsthal and Schneeburg, can lead to leukaemia or bronchial carcinoma These earlier reports had been reinforced by the incidence of leukaemia in the survivors from atomic bomb explosions at Hiroshima and Nagasaki and by the 0·3 per cent incidence of leukaemia in

patients irradiated for ankylosing spondylitis (Court-Brown, 1958), by the reported development of thyroid cancer in 10 out of 1502 children irradiated for "thymic hyperplasia" (Simpson and Hempelmann, 1957) and by an alleged increased death rate among American radiologists (Warren, 1956). The most worrying report had been that by Stewart even suggesting that diagnostic irradiation to the pelvis of pregnant women led to an increased incidence of malignant disease in their children.

Several more papers have appeared during the last year, some of them tending to allay our worst fears. Stewart, Webb and Hewitt (1958) have published a more definitive report suggesting that diagnostic x-irradiation of the pelvis in pregnancy does lead to malignant disease in the child, but in less than 0·1 per cent of those irradiated. Abbatt and Lea (1958) have published evidence suggesting that leukaemia is more common in patients with rheumatic diseases than in the general population, even when radiation treatment has not been given. Court-Brown and Doll (1958) have reassured the author, among others, that radiologists in England and Wales (who started practice after 1921) do not have either a shorter life or a higher mortality from cancer than their professional colleagues. Some extremely interesting preliminary experimental results have been described by Mole (1958) indicating that dose-rate does have an influence on induction of leukaemia in mice and that at low dose-rates there may be a very low or even no harmful effect. Finkel at the Seventh International Cancer Congress produced evidence on the induction of bone sarcoma in mice to the same effect, suggesting that there may even be a "threshold" for cancer induction. An extremely interesting report has also just appeared suggesting that there might be the same dose-rate dependence in radiation induction of genetic mutations (Russell and Kelly, 1958). The whole subject had been well reviewed by Lamerton (1958) who concluded that there was as yet little evidence that chronic irradiation at low doses has any harmful effect.

The clinician can perhaps conclude that each therapeutic or diagnostic use of radioisotopes needs to be separately evaluated in terms of the benefit to the individual patient in comparison with the radiation dose given to him and its possible harmful effects. It is as well to bear [illegible] of the foetus *in utero* (and probably in infants) th[illegible] car-cinogenesis has been demonstrated after [illegible] and children may develop cancer after *therapeutic irradiation at dose levels from* 100r. upwards, and much caution is needed in deciding to treat benign conditions such as naevi and eustachian lymphoid hyperplasia by radiotherapeutic methods. In adults it appears wise to reserve new methods of radioisotope treatment of benign conditions for the older age groups (say, over 45 years) and for those in whom surgery or other treatment is relatively dangerous, until each method has been in wide use for 10 or even 20 years and its carcinogenic hazards are better known

CONCLUSION

It is hoped that this brief review has not been too much of a catalogue of radio-isotope applications, and that some readers may be induced to try the attractive techniques now available, particularly in diagnosis and research, not all of which

need expensive and complex equipment. In treatment by far the most benefit is still being received from the wider use of megavoltage irradiation, as can be delivered from the large cobalt teletherapy units now being constructed, with caesium units a good second-best alternative Radioisotopes should now have an established place in the treatment of thyroid and blood diseases and less so in diseases of the eye and skin. They can also be of high value in interstitial and *intracavitary treatment of many types of malignant disease.*

It should be unnecessary now to emphasize that collaboration and consultation are needed between physician, physicist, radiotherapist and surgeon (listed in alphabetical order!).

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Cancer of the prostate

Evaluation of colloidal radioactive gold in treatment

ELKINS, FLOCKS and CULP (1958) describe the use of colloidal radioactive gold in the treatment of prostatic cancer The gold is administered by direct injection in a shielded syringe. The dose is 0 5–2·5 millicuries per gramme of tissue. With adequate diffusion the lowest dose delivers about 3,000 *gamma* r and 35,000 *beta* rep per gramme. Care should be taken to avoid overdistension of the seminal vesicles and rupture of the genital fascial envelope, for pooling of the radioactive material may lead to severe rectal complications. If excessive quantities of the colloid are injected into the prostate some of the solution may enter the blood stream, thereby subjecting the patient to unwanted radiation and decreasing the local effect. For the most part the injections should be used only when the disease is limited to the gland and the adjacent area. More conservative measures should be employed in the treatment of patients with a short life expectancy owing to senility or intercurrent disease. It is suggested that gold injections may be preferred to radical surgery if the disease is minimal. Among a series of 135 patients 32 were alive without clinical disease 5 years after receiving gold treatment. Five patients had survived with local recurrence of the disease and 9 patients had survived despite the presence of metastases. Complications comprised rectal ulceration, leucopenia, calculus formation and urethral stricture. By meticulous attention to technique the investigators were able to reduce the incidence of complications from 24 to 6·5 per cent.

Cancer of the cervix uteri

Radiogold in treatment

ALLEN, SHERMAN and CAMEL (1958) describe the use of radiogold in the management of cancer of the cervix If the category of the disease is either stage 1 or stage 2 the primary lesion is treated with radium, in a dosage of 4,000–5,500 milligram hours Two weeks later 50–70 millicuries of radiogold, diluted in 35 millilitres of physiological saline, are injected into each parametrium The effectiveness of the gold therapy is probably due to intense *beta* irradiation within the lymphatic nodes. If the patient's condition is satisfactory a Wertheim hysterectomy, with pelvic lymphadenectomy, is performed 4 weeks after the gold injections When the operation is contra-indicated a second radium application is usually required. As far as possible the total irradiation of the bladder and rectum is kept below 6,000 *gamma* roentgens. For stage 3 lesions no operation is performed but the maximal amount of irradiation is employed. The patient's reaction to radiogold therapy is minimal; diarrhoea does not occur and there is little or no nausea. During a period of 7 years 291 patients received radiogold treatment Complications included uretero-vaginal fistula (3 cases), vesico-vaginal fistula (2 cases) and ureteral obstruction (7 cases). Many patients experienced transient neuritic pain owing to irradiation of the obturator nerve and sacral plexus. Removal of diseased pelvic lymphatic nodes enhanced the survival rate in stage 2 cases The salvage rate with radiogold treatment was appreciably better than the rate in patients treated with x-rays and radium.

Cancer of the breast

Radioisotope therapy of internal mammary lymph nodes

Discussing the use of isotopes in the management of breast cancer, BRASFIELD and HENSCHKE (1958) describe the treatment of the lymphatic nodes situated in the vicinity of the internal mammary artery. At the conclusion of radical mastectomy, but before the skin flaps are closed, a transverse incision is made in the first intercostal space on the affected side and the internal mammary vessels are exposed. The internal mammary artery is ligated and a slit is made in the vessel just below the ligature. A thin nylon tube with a closed end is introduced into the artery and threaded as far as the xiphoid process.

The artery is ligated below the slit. The other end of the tube is threaded through a large-bore hypodermic needle. Radioactive substances such as ^{192}Ir, ^{60}Co and ^{182}Ta are introduced into the tube No complications developed when the authors employed doses of 9,000r, or less, in the treatment of 19 patients.

Ovarian cancer

Routine intracavitary administration of colloidal ^{198}Au

MULLER (1958) presents an account of the routine intracavitary administration of

isotope combined with saline solution. Provided that there were no adhesions to cause loculation of the fluid the technique was found to be safe for patient and surgeon alike. The results of treating a series of 51 unselected patients were assessed after a period of

and after the injection of the isotope in a dosage of 70–150 millicuries survival was recorded in every instance. Among 13 patients with bilateral ovarian tumours or with

therapy. There were no survivors among the other patients

the disease had reached a

Heidelberg techniques of contact irradiation with ^{60}Co

BECKER and SCHEER (1958) report on their techniques of contact irradiation with ^{60}Co For intracavitary irradiation 4-millicurie beads of the isotope are threaded on silk and introduced through tubes of narrow bore If the cavities are relatively large the size of the chain is increased by the addition of inactive plastic beads. In the treatment

a dose of 10,000r. was well tolerated. Beads were employed in the treatment of 497 cases of carcinoma of the urinary bladder. Surface doses ranged from 6,000 to 12,000r. Five of 38 patients survived for more than 5 years. Carcinoma of the body and cervix of the uterus is treated by intracavitary packing with ^{60}Co beads combined with intravaginal plastobalt mould. Plastobalt mould treatment of vulval carcinoma has now been abandoned in favour of electron beam irradiation from a betatron.

Epidermoid carcinoma

Effect of cobalt-60 beam therapy

SMITH and LOTT (1958) report on the advantages of cobalt-60 teletherapy over conventional x-ray therapy. The former technique yields more penetrating radiation, decreased skin reactions and a lessened systemic effect. In cases of oral carcinoma, tumour invasion of the mandible can be controlled by the cobalt treatment. When the disease has invaded the adjacent solitary lymphatic nodes the treatment may produce a favourable local response provided the nodes are incorporated in the treatment volume. Cobalt-60 teletherapy may prove to be effective when malignant disease recurs despite the use of x-ray therapy. Doses ranging from 6,000r. in 4 weeks to 7,500r. in 6 weeks were employed in the treatment of 50 cases of oral carcinoma. The incidence of bone necrosis was minimal with this dosage. Furthermore, severe skin reactions were fewer than in cases treated by x-rays. During a period of 3 years 13 patients with epidermoid carcinoma of the larynx were given ^{60}Co therapy. These cases were not considered to be suitable for laryngofissure and cord excision. In 6 cases there were signs of subglottic extension of the growth. Twelve patients remained free from carcinoma for periods ranging from 1 year 9 months to 5 years. With reference to oesophageal cancer it was found possible to use relatively large doses of radiation with ^{60}Co. Severe complications were not of sufficient frequency to warrant a change of policy in potentially curable cases. As for carcinoma of the bladder, tumour doses were within the range of 6,000–6,500r. administered during a course of 6–6½ weeks. At this dosage the degree of dysuria was usually only moderate. Better results were obtained in cases of small papillary lesions of the transitional cell variety than in low-grade squamous-cell carcinoma showing evidence of ulceration, infiltration and infection.

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PROGRESS IN THE CASUALTY DEPARTMENT

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INTRODUCTION

Eight years ago the General Infirmary, Leeds, made the experiment of appointing a medical officer of consultant status to the Casualty Department in the expectation that experience applied at the earliest moment would result in saving of sickness absence for the patient, and also of hospital resources Not only should there be better diagnosis of the major surgical emergency, there should also be a higher standard of care for the so-called minor injury.

A Consultant Surgeon in charge of Casualty by example, teaching and constant supervision should be able to achieve this, besides finding the task a challenge to his technical skill and moreover one of absorbing interest. In the General Infirmary at Leeds about 2,000 lacerated hands are treated each year. If the standard of treatment could be raised so that, on average, each case is made fit for full work one week sooner, the saving to industry of man-hours and to the hospital of materials should be very great.

In the treatment of superficial abscesses a new method involving precise timing relations between the administration of the antibiotic and the operation has been devised which saves in-patient treatment and eases the pressure on hospital beds. With close supervision of treatment in the ancillary departments, sprains and other so-called minor joint lesions can be treated with a minimum period of disability. In the ensuing sections, the principles of out-patient treatment of two kinds of frequently occurring emergency cases are described, together with a less common but important injury due to modern household machinery.

TREATMENT OF THE ACUTE ABSCESS

Long before the appearance of penicillin-resistant organisms, the treatment of the acute staphylococcal abscess by penicillin was found to be most disappointing. Penicillin rarely cured and usually at best it merely retarded the growth of the abscess and diminished the surrounding cellulitis. It was observed in the Casualty Department at Leeds General Infirmary, however, that in those patients who had had several days' pre-operative penicillin, after the operation of incision and drainage healing was much more rapid It occurred to the author that if, after the pus

had been gently evacuated, the lining barrier of granulation tissue was broken the penicillin could enter the cavity and attack the infection directly. It was postulated that the granulation tissue barrier surrounding the abscess not only prevented the infection inside the abscess spreading to the surrounding tissues but also prevented substances, such as penicillin, from entering the abscess from the surrounding tissues. If penicillin could enter the cavity in high enough concentration, its bactericidal action should overcome the infection. With this achieved, the result should be a sterile wound and primary suture would be possible.

Routine of treatment

The following routine was therefore devised for the treatment of all superficial abscesses. One-half to one hour before the time for operation, a large dose of penicillin was injected (premedication for a general anaesthetic could be given at the same time). At operation, the abscess cavity was adequately opened, all pus, slough or other dead tissue were evacuated. The lining wall of the cavity was gently curetted with a Volkmann's spoon or abraded with gauze until it was oozing blood all round The cavity was then obliterated with deep sutures, all blood clots having been evacuated, and the wound firmly closed The wound was inspected on the fourth day, a further large injection of penicillin having been given in the interim. It was found that the wound had healed by first intention.

This treatment was started in the middle of 1950. When a large number of case had been treated and healing had occurred, the bacteriologists were asked to investigate the exudates for the possible bacteriological confirmation of the empirical clinical theory. Acting with Dr. C. M. Williamson of the University of Leeds Bacteriology Department, pus was withdrawn from a series of abscesses (unselected save in so far that they were large enough) by a trocar and cannula just prior to operation After evacuation of the pus and curettage, the blood oozing into the cavity was also withdrawn. An assay of penicillin concentration in this pus and blood was made. In no instance in this series of over 20 cases was any penicillin detected in the pus, but in the blood there was always a high concentration of the drug

Failure of primary healing

In the 8 years in which this routine of treatment has been carried out, primary healing has been expected in all types of superficial abscesses. The following factors prevented primary healing in certain cases:

Failure to evacuate all pus and dead tissue

(1) In multi-locular abscesses, failure to discover all loculi allowed the abscess to reform. A breast abscess is commonly multi-locular and an ischio-rectal is not infrequently so Particular care is required in such cases

(2) In infected hands, the formation of slough is common Special nibbling forceps are now used to detach all slough from the walls of the cavity, for the attachment is often too tough to allow it to be detached by a spoon.

(3) Bone sequestra in infected hands must be removed as soon as discovered.

Necrosis of skin

When an abscess has grown so large as to point through the skin, this skin has poor viability. The sutures obliterating the cavity may cut through such skin and the actual skin wound will gape to a greater or lesser extent. Healing is delayed whilst this superficial ulcer is epithelialized.

Insensitivity of the organisms to antibiotics

In the majority of cases coming in "from the street", penicillin insensitivity has scarcely been a cause of trouble. In breast abscesses, when the mother has been delivered in hospital, insensitivity to penicillin and then to streptomycin appeared over the years At the present time, intramuscular terramycin is used pre-operatively in breast abscesses.

In ischio-rectal abscesses, from the beginning allowance was made for the possible presence of insensitive bowel organisms and a mixture of antibiotics has always been used.



(a)



(b)

FIG 89. — (a) Ischio-rectal abscess Finger showing size of cavity stretching posteriorly. Note the anus just covered by the towel, (b) finger reaching forward to perineum



FIG. 89 (cont'd).—(c) Hagedorn needle completely encircling the cavity, (d) wound firmly closed with two mattress sutures.

(c)



(d)



FIG. 89 (cont'd).—(*e*) Sixth day showing sound healing

(*e*)

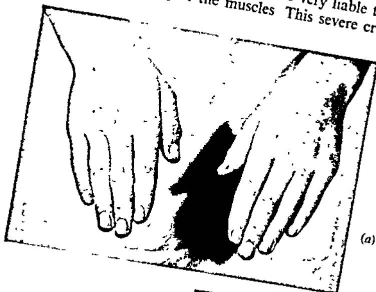
It is in the treatment of peri-anal and ischio-rectal abscesses that this plan has effected a radical improvement over the time-honoured method The accepted routine with an abscess of any size was to admit the patient to hospital. At operation, the skin over the abscess was cut away widely and the cavity packed with gauze and left to granulate. This required up to 6 weeks in hospital. The repacking of the wound was usually so painful that an anaesthetic was required. All patients with ischio-rectal abscesses in this department are now treated as out-patients. Figs. 89*a* and *b* show an abscess cavity 2 inches in diameter. The insertion of the deep sutures and sutured wound are shown (Figs 89*c* and *d*) Fig 89*e* shows the well-healed wound on the sixth day, 2 days after the removal of sutures. In the last 4 years 514 cases have been treated in this department with an average saving of hospital bed days of at least 2 weeks each The population of the country is about 100 times that of Leeds. The immense saving of hospital beds if this treatment were generally adopted is obvious Since the publication of this method (Ellis, 1951, 1953), some other hospitals are carrying out the treatment. In a criticism of a book by Lowden (1955) in which this method of primary suture is described, Ogilvie (1955) suggested that it would not be suitable for younger surgeons A large proportion of these operations are carried out in the author's department by Junior Residents, who have been qualified for 1–2 years They learn the technical details described above very quickly and their results are comparable to those obtained by more experienced surgeons.

WRINGING MACHINE INJURIES

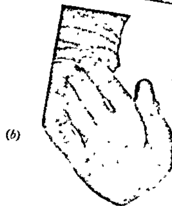
In 1950, Hausmann and Everett described a series of cases in which the upper limb was damaged by its being drawn in between the rollers of the automatic wringing machine, commonly attached to electric washing machines In Great Britain, electric washing machines are widely used and an automatic wringer is fitted to a large proportion of them. A steady stream of injuries to the upper limb is now appearing in all Casualty Departments The injuries are usually in small children, assisting mother with the weekly wash. When the mother's back is turned, the child feeds clothes into the automatic wringer If the hand is caught between the

rollers, the rest of the upper limb is drawn in to a distance depending on how quickly the "trip" mechanism which separates the rollers is put into action.

Hausmann and Everett described the torn muscles and fractures they had seen in such cases. In the author's department the only case of an open wound with such injuries was in a washing machine demonstrator. There has been no instance of fracture. However, these cases are very liable to serious complications due to the severe crushing of the muscles This severe crushing of the forearm muscles



(a)



(b)



FIG 90—(a) Wringing machine injury. Hands in neutral position showing no apparent deformity; (b) hands in full extension showing flexion contracture.

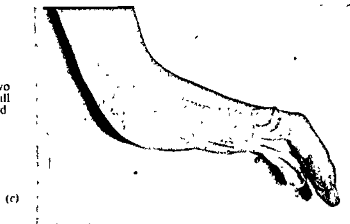
may produce local or general ischaemia. In one case, 2 weeks after the injury, the skin broke down and a small slough was extruded from the bellies of the forearm muscles. More commonly the ischaemia leads to a contracture very similar in effect to Volkmann's ischaemic contracture. This complication is not mentioned by Hausmann and Everett. A typical early contracture is shown in Figs. 90*a* and *b*. This injury occurred in a boy aged 15 years whose forearm was crushed up to the elbow between the rollers The photographs illustrate that unless such a contracture is specially sought by full extension of the wrist and

fingers, it can very easily be missed. Five more similar instances of contracture have been seen in over one-hundred wringing machine injuries.

Treatment

The treatment of these injuries is now based on the known possibility of the occurrence of ischaemic complications. As soon as the patient is brought into the department, wet compresses are applied to the forearm and the limb is kept at rest

FIG 90 (cont'd) —(*c*) Two months later deformity still present, (*d*) deformity cured



(*c*)



(*d*)

in a sling. To overcome the ischaemia, short-wave diathermy which causes dilatation of the deep vessels, is applied to the proximal part of the limb This treatment is carried out twice daily at the beginning After 4 days, the movements of the fingers and wrist in hyperextension are carefully checked In the case illustrated the contracture was discovered on the fourth day Since one case manifested itself on the tenth day, diathermy is continued for at least 14 days in all cases.

If a contracture is seen to be developing, the passive stretching exercises of the fingers and wrist are immediately started The patient or the parents are instructed in these exercises and are asked to carry them out at home at least 2-hourly The

patients visit the Physiotherapy Department daily. By means of this regime, no residual deformity has occurred in these 6 patients The treatment is necessary for many weeks and the illustrations show the progress of the case described and its end result after 4 months (Figs 90*c* and *d*)

THE TREATMENT OF BURNS IN THE CASUALTY DEPARTMENT

In Leeds General Infirmary about 700 burned patients every year come to the Casualty Department. Out of this number some 40 to 50 burns can be classed as serious, that is, involving danger to life from the associated shock. The advantages of having a Consultant in charge of the Casualty Department are that authority and experience can be used to summon the in-patient emergency surgical staff to start the treatment of such cases by transfusions without any delay. This still leaves some 650 burned patients to be treated who do not require transfusions. It is obvious if all these can be treated as out-patients, the saving in hospital beds will be very considerable Some of these burns are quite small in area and are relatively trivial and will cause no difficulty in any department. But there are those of considerable area, not big enough to require anti-shock treatment, which demand more elaborate treatment. It is the aim of this department to treat all such patients as out-patients

In the local treatment of the burned area there are three desirable requisites: (1) to minimize or abolish the pain, (2) to prevent infection, (3) to allow healing to occur in the minimum possible time without scarring. If these three can be achieved, in young children in particular, the psychological benefit of being looked after by their own parents in their own home should not be underestimated. A Leading Article (1953) suggested that the open treatment of burns could not be carried out in the home. Our experience in the Casualty Department over the past 7 years has shown that the advantages of treating burns by the open method at home far outweigh the disadvantages Treatment of these larger areas by the closed method in the home may allow the bandages to work loose so that infection may be trapped in the burn In the open treatment of the burn, if the crust cracks and there is an exudation of serum, the organisms settling on this serum from the atmosphere in the home are still probably sensitive to antibiotics Infection can then be prevented or minimized. If similar large burns were nursed in hospital by the open method, organisms settling on the broken crust are all too commonly insensitive to antibiotics and infection is difficult to prevent or control. Not only will the infection delay healing, but it will also serve as a source of contamination for other wounds in the ward. Experience over 7 years has shown that burns treated by the open method in the home have not been significantly affected by infection

Details of treatment

As soon as a non-serious burn arrives in the department, a special paint, consisting of a gentle tanning substance (Neosyn) made up in gum acacia, is painted over the burned area with a sterile brush. No routine toilet of the wound is carried out. But if a greasy application has been previously applied, this is removed with

1 per cent cetrimide before painting. Small blisters are ignored but the contents of large blisters are gently squeezed out with sterile gauze before painting. A frequent first aid application in this area is bicarbonate of soda and this has been found to combine well with the paint. The burned area with its paint is then left to dry. This usually takes about half an hour. A prophylactic injection of penicillin



FIG 91.—(*a*) Burn on side of neck and chest due to boiling fluid from overturned pan The dry crust the day after the injury is shown, (*b*) 12 days later, showing crust detached, no scarring.

(*a*)



(*b*)

is given. The patients or relatives are instructed to keep the burned area uncovered and exposed to light and air. The senior nursing staff take considerable pains in explaining and demonstrating how to arrange the clothes and the bed-clothes to achieve this. Occasionally a bed-cradle is loaned to the patient. All patients are seen the following day. Any moist areas are repainted and redried. A further injection of penicillin is given. Thereafter the patient is seen at increasing intervals according to the response to treatment. The crust and the paint begin to separate from 7 to 10 days later and no washing is allowed until it is evident that the crust is definitely loose.



(*a*)



(*b*)

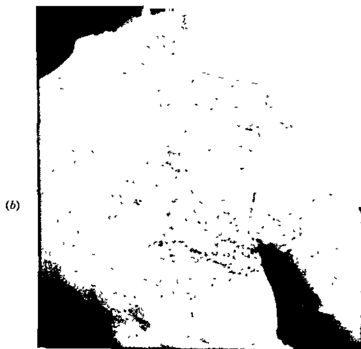
FIG. 92.—(*a*) Burns of face due to blow-back from boiler; (*b*) 20 days later.

It has been found as an empirical observation that in the majority of instances this paint relieves the immediate pain of the burn An all too common burn (or scald) coming to the department is that in a small child who has pulled over a pan of hot liquid on to the neck and chest (Fig 91*a*). These children arrive in the [illegible] them to sleep in the [illegible] illustrated in Fig 91*a*



(a)

FIG. 93.—(a) Burns of back showing crust over large area of third degree burn the day after injury; (b) third degree burn 4 months later after grafting



(b)

was nursed at home and the result on the twelfth day is shown in Fig 91*b*. Another common burn in industrial areas is that resulting from the stoking of a boiler. The stoke-hole is left open and a gust of flame bursts out causing burns of the face, hands and forearms. Fig. 92*a* shows such a burn the day following the incident. The lack of distress in the patient's face is noteworthy. The good end-result 20 days later is shown in Fig. 92*b* This man was treated as an out-patient and the total time spent by the nursing staff in looking after him, drying the paint, injecting the penicillin and giving instructions did not exceed half an hour.

Of course, some burns are in fact third degree with a destruction of skin. Not all the area is usually third degree and part of it may have some surviving epithelium When the crust over the second degree burns separates from the seventh to the tenth day, the crust over the third degree area becomes well demarcated. Under anaesthetic this crust can be cut away and the area prepared for a graft. The production of quite large split thickness skin grafts is relatively simple by the use of the electric dermatome. Fig. 93*a* shows a very large area of back and shoulders which was largely third degree burn in which grafting was carried out as an out-patient. It is admitted that such a large area would not normally have been considered as suitable for out-patient grafting, but as this patient was particularly keen not to be admitted to hospital, the undertaking was considered justified. The grafting was done in three sessions and Fig 93*b* shows the end-result some 4 months later It is suggested that if such results can be achieved with so large an area of burn, there should be no hesitation in treating smaller areas by the open treatment and any necessary skin grafting also as an out-patient.

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ABSTRACT RELATING TO PROGRESS IN THE CASUALTY DEPARTMENT

THE HAND

Septic-hand surgery

[illegible] of post-operative penicillin

[illegible]

taken [illegible] performed under general anaesthesia and a pneumatic tourniquet was [illegible] made in the line of a skin furrow. Septic blisters [illegible] ed and a portion of the [illegible] ved in cases of onychia.

ABSTRACT

An antero-posterior incision was employed for opening abscesses of the web-space. Pus and slough were removed by mopping or excision. Abscess cavities were inspected by direct vision and all loculations were opened. After the operation some patients were given oral penicillin in divided doses amounting to 1,200,000 units daily. Other patients received depot penicillin, 1 millilitre, by intramuscular injection. The solution contained procaine benzylpenicillin, 300,000 units, and sodium benzylpenicillin, 100,000 units.

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